VOLUME 58 • NOVEMBER 1957 • NUMBER 5

AMA ARCHIVES OF

OPHTHALMOLOGY

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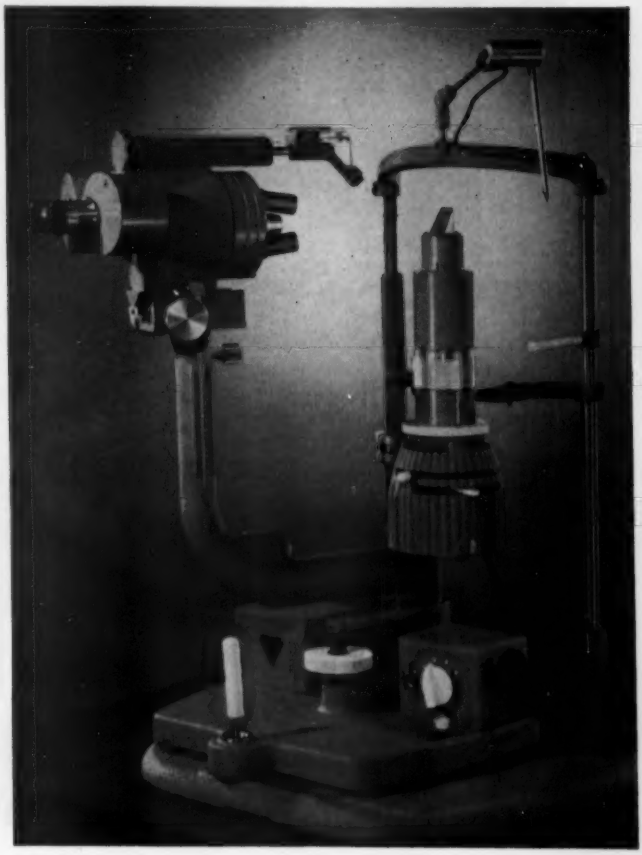

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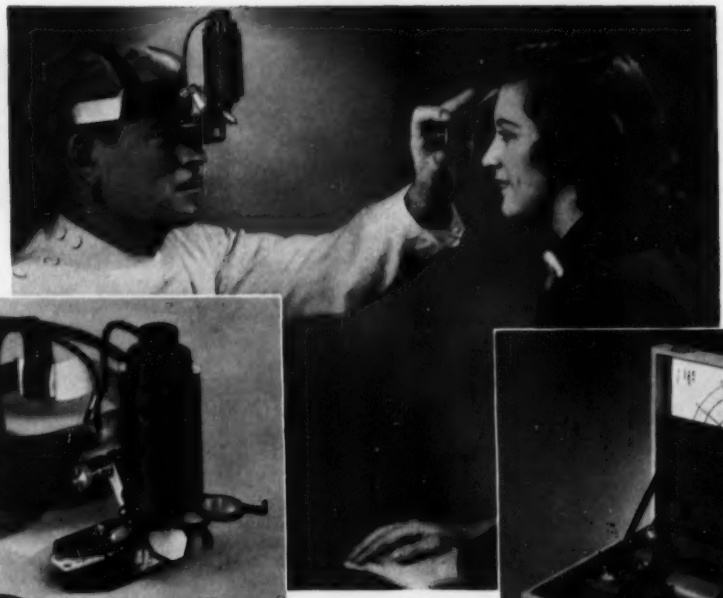

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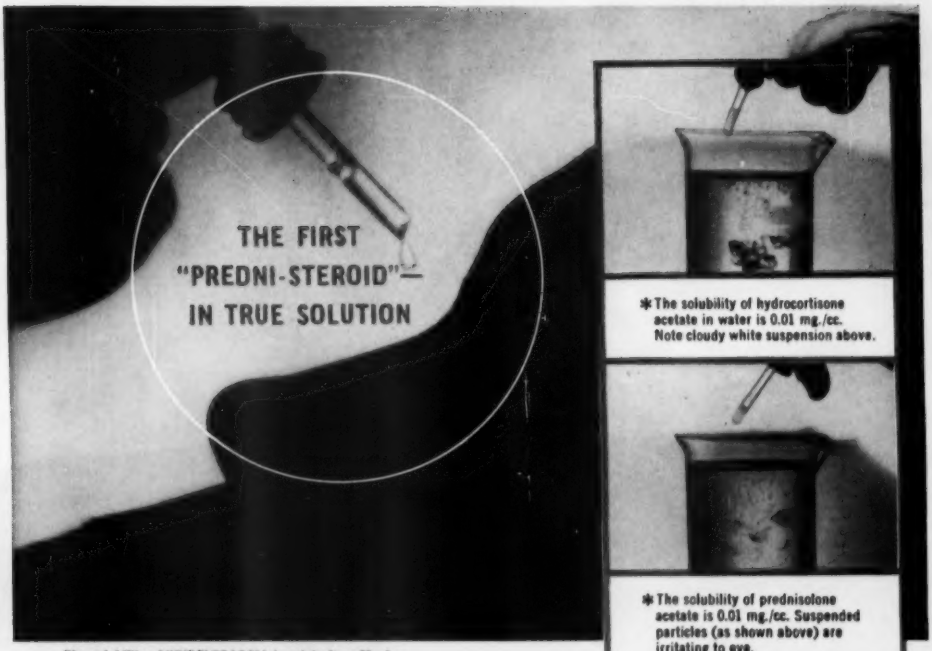

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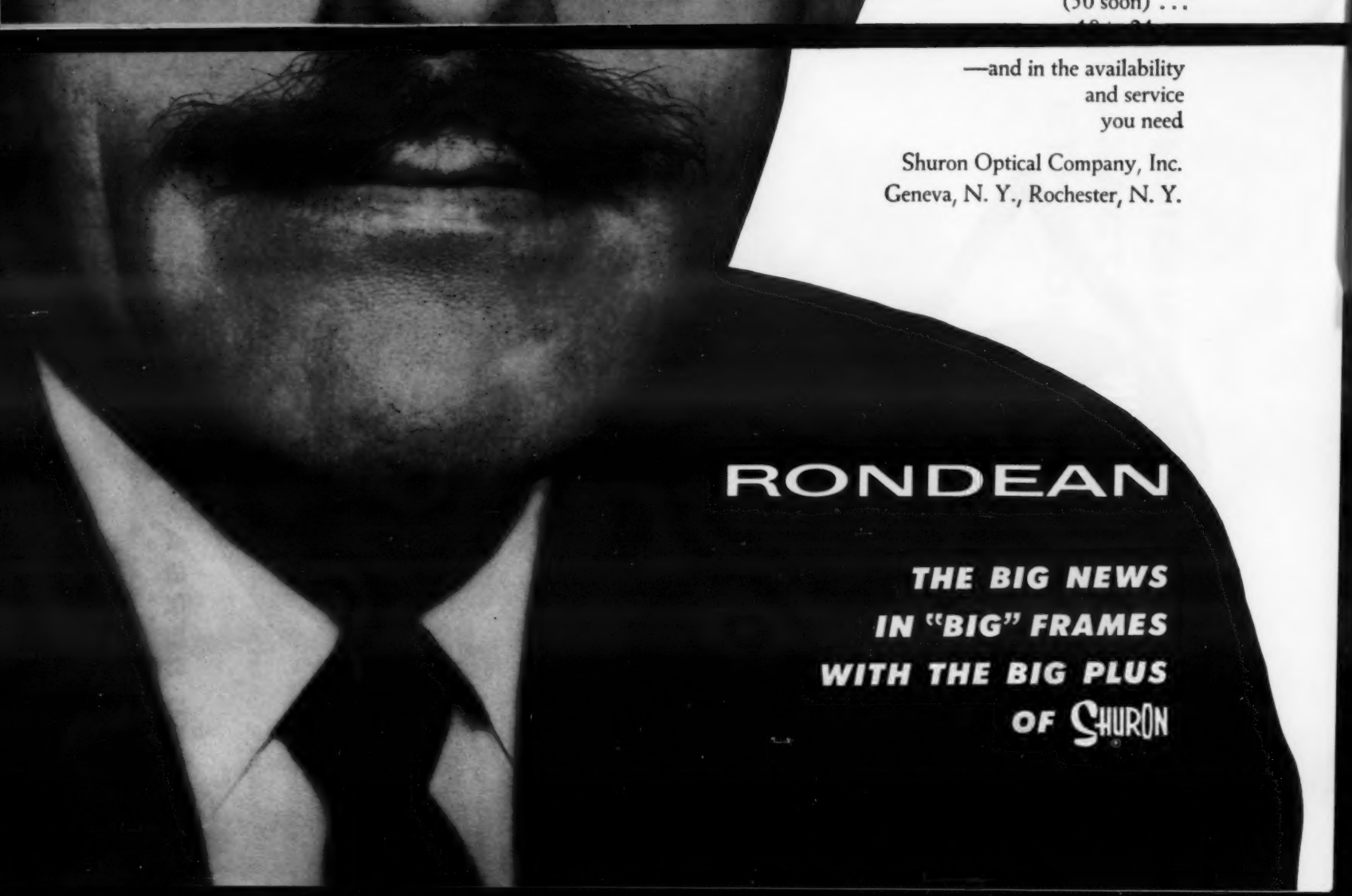

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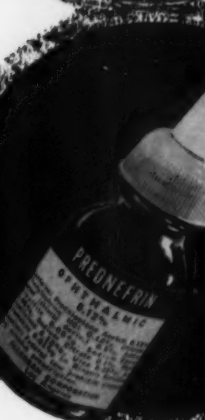

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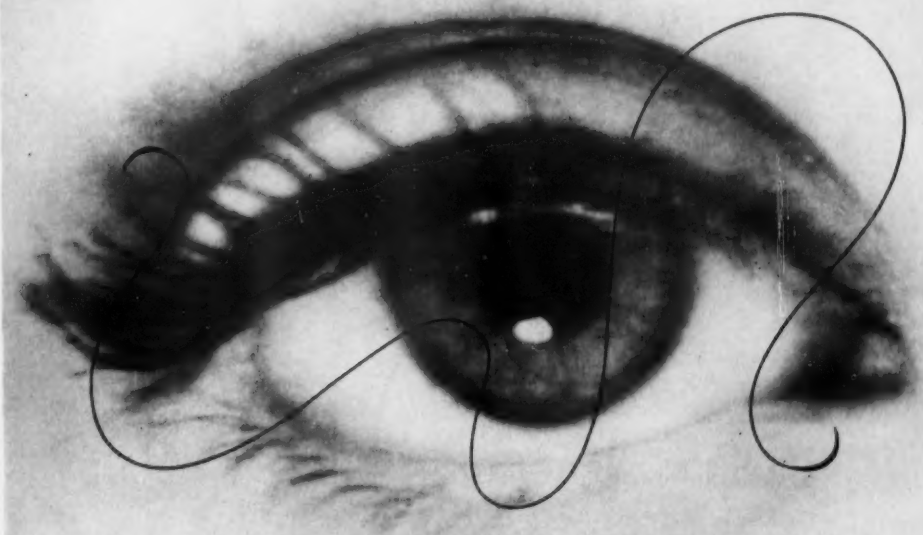

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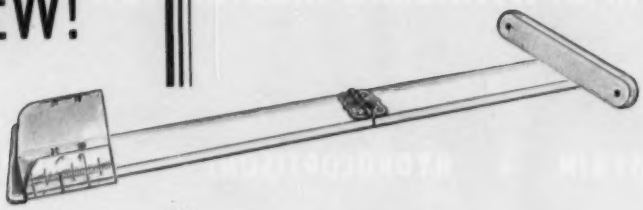

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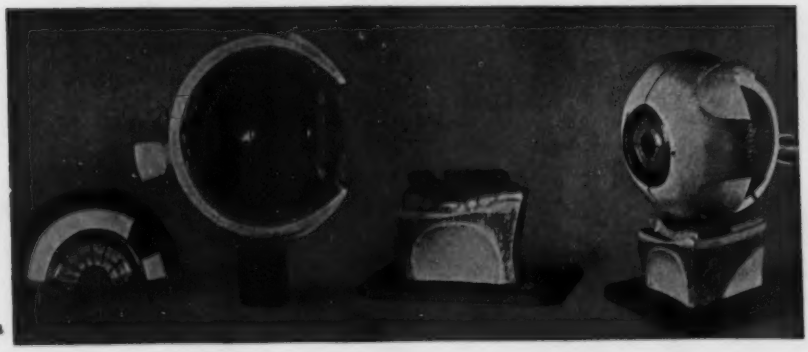

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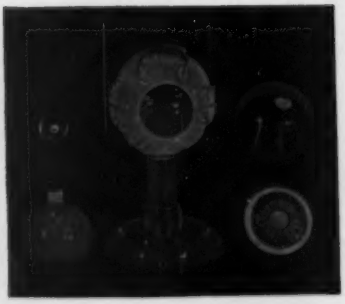

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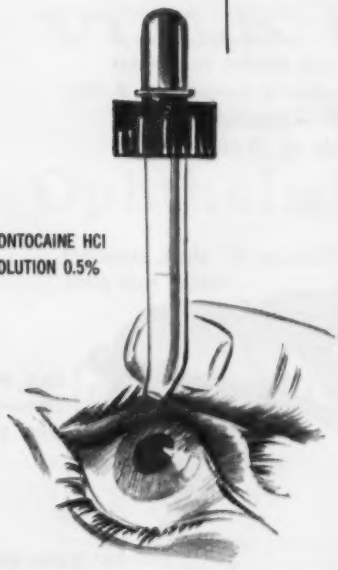

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The Nature of Vergence Revealed by Electromyography

II. Accommodative and Fusional Vergence

GOODWIN M. BREININ, M.D., New York

This paper is one of a series of studies in vergence investigated by means of electromyography, parts of which have been previously reported.[1,2] The present study is concerned with accommodative and fusional vergence.

The technique has been fully described in previous reports.[1-4] The energy levels of various positions have been determined with the integrator. I have deliberately inserted electrodes into only one muscle in many cases to minimize artefacts induced by multiple needle placements. The latter is a definitely limiting factor in evaluating fusional amplitudes and is conducive to blurriness of vision in the tested eye. Nevertheless, simultaneous studies of both medial and lateral rectus confirm the findings to be reported. The lateral rectus has often been selected for testing because the question of divergence is of considerable interest and because there is thus little interference with vision or examination. In some studies very fine electrodes (No. 31 needles) were used. These are less traumatic but at many times may undergo displacement. No lid speculum is necessary, but care should be exercised to avoid artefacts of lid pressure.

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Department of Ophthalmology of the New York University Postgraduate Medical School.

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A. Approximation Vergence

1. *Binocular Fixation.*—When a fixation object is binocularly viewed in the midline, the convergence necessitated is manifested by an increased innervation to the medial recti, with a concomitant decrease of innervation to the lateral recti. When the fixation object is smoothly approximated to the eyes in the midline, eliciting either accommodative or fusional convergence, or both, at the moment when the near point of convergence is exceeded there is an increased innervation to the lateral rectus of the diverging eye, with a reciprocal inhibition of its medial rectus (Fig. 1). At this point, the fixing eye shows almost no change in the level of innervation of either lateral or medial rectus, despite the fact that the diverging eye may undergo greater and greater divergence. The same phenomenon may be noted when an object is smoothly approximated in the fixation axis of one eye, i.e., by an asymmetric convergence. In this instance, the lateral and medial recti of the eye toward which the object is being approximated show almost no change of innervation (Figs. 2 and 3). The eye which is undergoing the burden of movement,

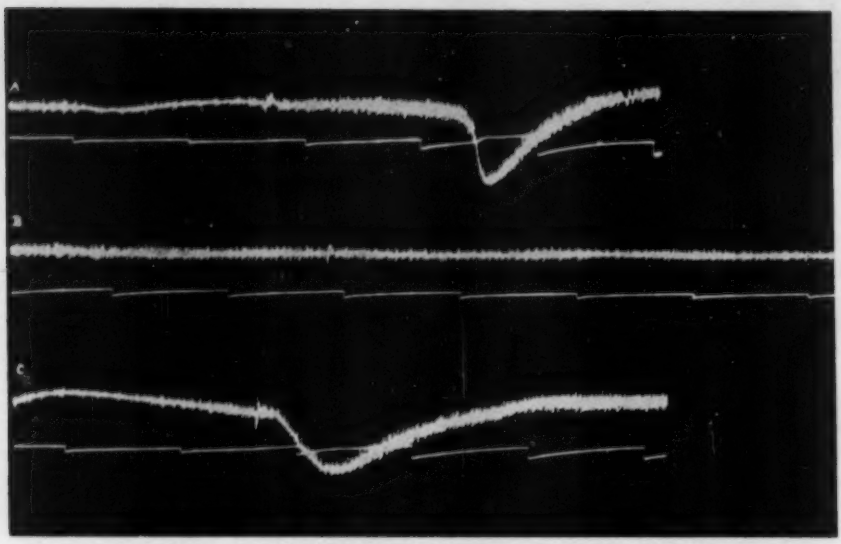
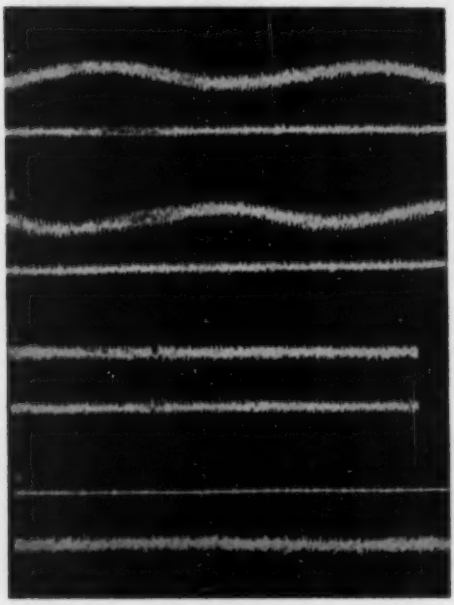


Fig. 1.—Divergence from NPC. Right lateral rectus, upper trace; integrator, lower trace. *A*, convergence to NPC with break into divergence; *B*, converging; *C*, divergence, active.

Fig. 2.—Approximation vergence. Left lateral rectus, upper trace; left medial rectus, lower trace. Approximation in axis O. S.: *A*, start; *B*, end (no change—O. S. stationary). (Undulation of upper trace is an artefact.) Approximation in axis O. D.: *C*, start; *D*, end (change—O. D. converged).



however, shows the expected large alterations of innervation (Figs. 2 and 4). This has been previously described.[2]

In studying asymmetric convergence in a group of normal persons it has been a frequent finding that when the near point of convergence has been exceeded there is a lateroversion of the ipsilateral eye (Fig. 3). In other words, the increasing convergence innervation must be neutralized by an increasing lateroversion innervation in the eye toward which the object is being approximated. This eventually may preponderate over fixation, forcing the ipsilateral eye into an actual lateroversion movement. This is further evidence for the compound nature of such movements. As a result, the innervation of the horizontal recti of the ipsilateral eye will show no change up until the near point of convergence (NPC), at which point an increase of lateral rectus firing and reciprocal decrease of medial rectus firing initiates the lateral movement. At no time is there a simultaneous increase in the innervation of both medial and lateral rectus of the ipsilateral eye. The reciprocity mechanism is thus always in evidence. It is of interest that at the moment the ipsilateral

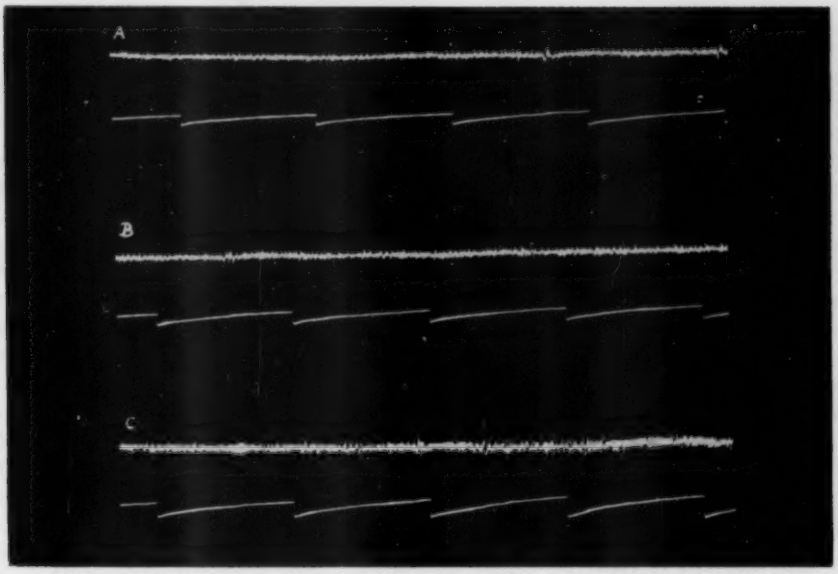
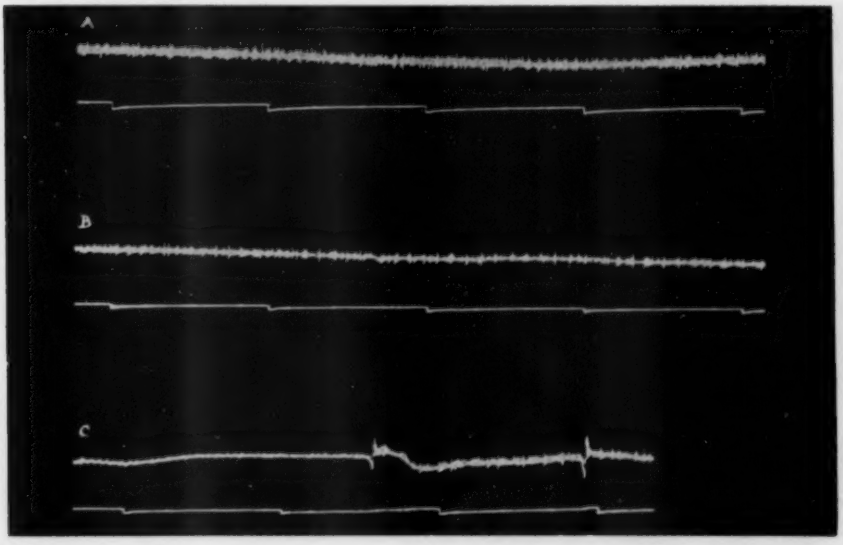


Fig. 3.—Approximation vergence. Right lateral rectus, upper trace; integrator, lower trace. Approximation in axis O. D.: *A*, start; *B*, near end (no change); *C*, version.

eye gives up fixation it appears to be involved in a conjugate movement with the opposite eye. It should be pointed out that these movements are induced by a smooth approximation of a fixation object along the fixation axis of one eye. The experiment in which two fixation objects are placed at different distances in the axis of one eye and

Fig. 4.—Approximation vergence. Right lateral rectus, upper trace; integrator, lower trace. Approximation in axis O. S.: *A*, start; *B*, middle (decreases as eye converges); *C*, end, with divergence.



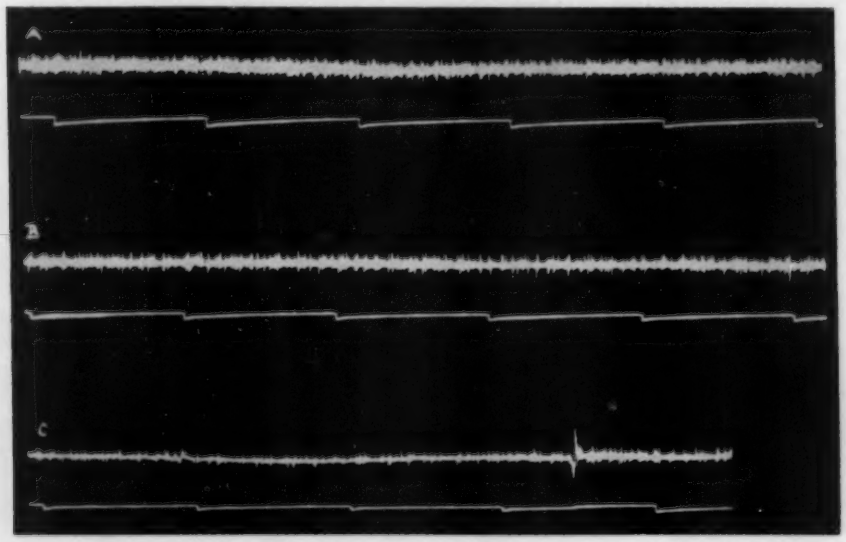
the subject directed to look first at one and then the other is not comparable, for in this instance there is a discontinuity in the adjustment of innervation. As a result, there usually occurs first a version movement of both eyes followed by a convergence, and so the end-result is the same. The fractionated nature of the dual movement, however, is immediately apparent to the naked eye. No special methods of observation are required to note this simple clinical fact, although it is readily recorded and analyzed by the electro-oculogram [5] or optical devices.[6] Similar findings are noted in prism jump experiments, where discrete increases of prism power are placed before one eye. There is no opportunity in these examples for smooth adjustment of innervation, and a dual movement is exhibited.

2. *Monocular Fixation.*—If asymmetric convergence is repeated, this time with only one eye fixing and the other eye covered, identical findings are obtained. In this instance, we are dealing with the effects of accommodative vergence, although the proximal factor may also be involved. In the previous instance, with both eyes fixing, we had fusional vergence as well. Again, the fixing eye shows no change in its innervation, whereas the occluded eye shows the expected alteration.

B. Prism Vergence

In order to isolate the phenomenon of fusional vergence, a haploscopic device or prisms may be used. In the case of prisms placed before one eye, we find comparable results, namely, the eye before which prisms are placed and which consequently undergoes a deviation shows the expected alteration of innervation to the horizontal muscles. That is, with base-out prisms the medial rectus augments while the lateral rectus decrements. When the fusional limit is passed a divergence burst occurs (Fig. 5). At the same time, the eye which is fixing without prisms and which hence undergoes no movement exhibits no change in its innervation as prismatic power is gradually increased until the limit of fusion is reached and diplopia occurs (Fig. 6). At this point one occasionally sees a lateroversion of the eye which is fixing without prisms. In other words, the increasing prismatic convergence innervation forces greater and greater amounts of lateroversion in-

Fig. 5.—Prism convergence. Right lateral rectus, upper trace; integrator, lower trace. Prisms before O. D. *A*, start; *B*, middle, decreasing; *C*, end, with divergence.



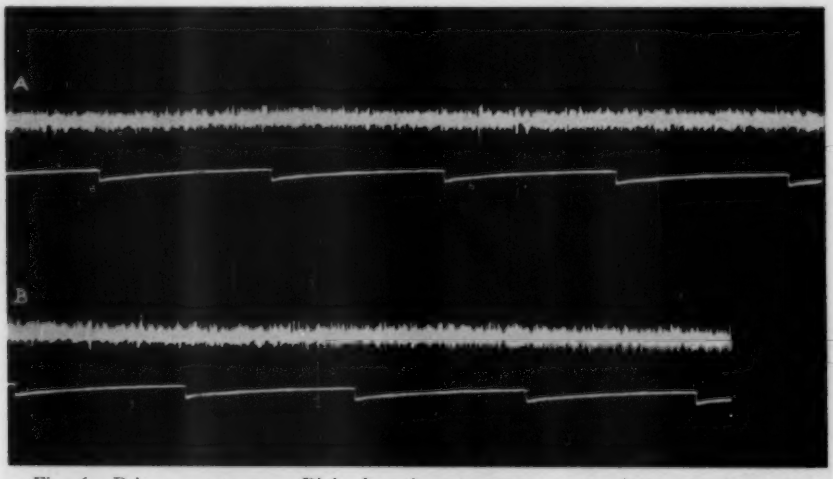


Fig. 6.—Prism convergence. Right lateral rectus, upper trace; integrator, lower trace. Prisms before O. S. *A*, start; *B*, end (no change).

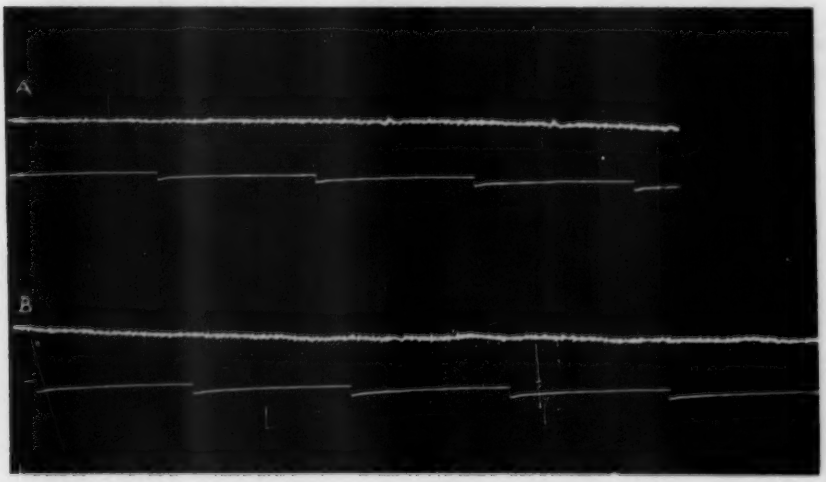
nervation upon the contralateral eye until, when fusion is exceeded, the version impulse preponderates and it rotates out. There is, thus, an entirely analogous situation in the case of prismatic deviations.

C. Haploscope Vergence

The same experiment can be carried out with the use of a haploscope. When the patient is seated at the major amblyoscope and both tubes are converged or diverged symmetrically, there is the expected symmetrical alteration of the innervations. When fusional convergence is exceeded, there may be a divergence movement of one eye with an increased discharge of its lateral rectus and decreased discharge of its medial rectus.

Fusional amplitudes measured from the dissociated position show that a true active divergence does occur which cannot be con-

Fig. 7.—Haploscope vergence. Right lateral rectus, upper trace; integrator, lower trace. Symmetrical divergence. *A*, start; *B*, end, increases.



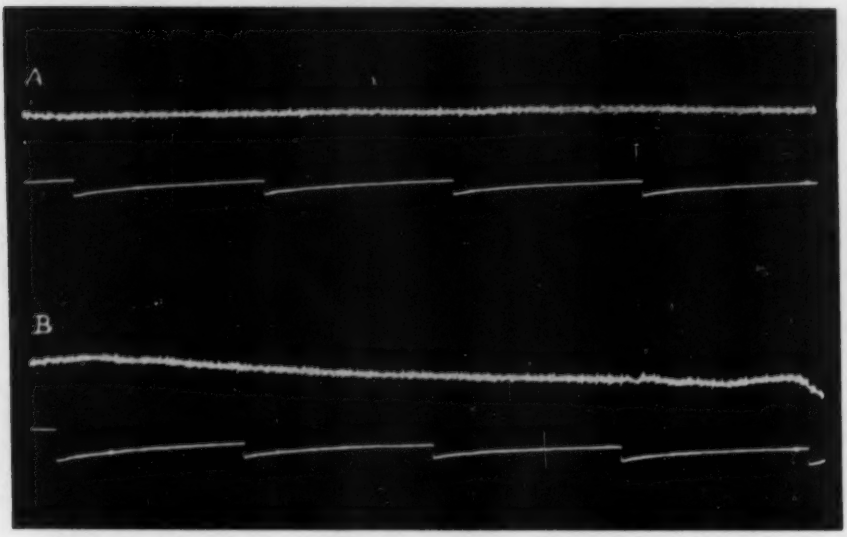


Fig. 8.—Haploscope vergence. Right lateral rectus, upper trace; integrator, lower trace. Asymmetric convergence. O. D. stationary. *A*, start; *B*, end (no change).

strued as a relaxation of convergence (Fig. 7).

If only one tube is converged while the subject binocularly fixates the targets, the situation is that of asymmetric convergence. Again, the stationary eye shows almost no change in its medial and lateral rectus innervation (Fig. 8), whereas the other eye, following the target, experiences the appropriate changes of innervation. As the convergence is continued there comes a point where fusion is exceeded and the patient becomes aware of diplopia. The diverging eye exhibits a burst of innervation to the lateral rectus (Fig. 9). It is occasionally noted that the eye which previously had not moved may undergo a lateroversion, exhibiting the necessary increase of innervation to its lateral rectus and inhibition of its medial rectus. Asymmetric divergence exhibits similar findings (Figs. 10 and 11).

Fig. 9.—Haploscope vergence. Right lateral rectus, upper trace; integrator, lower trace. O. S. stationary. Asymmetric convergence. *A*, start; *B*, end, with divergence, decreases until active divergence occurs.

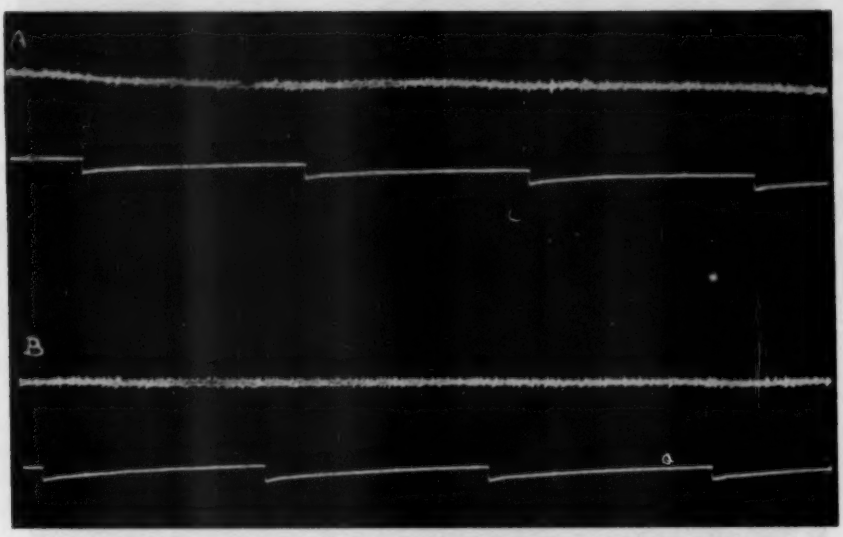


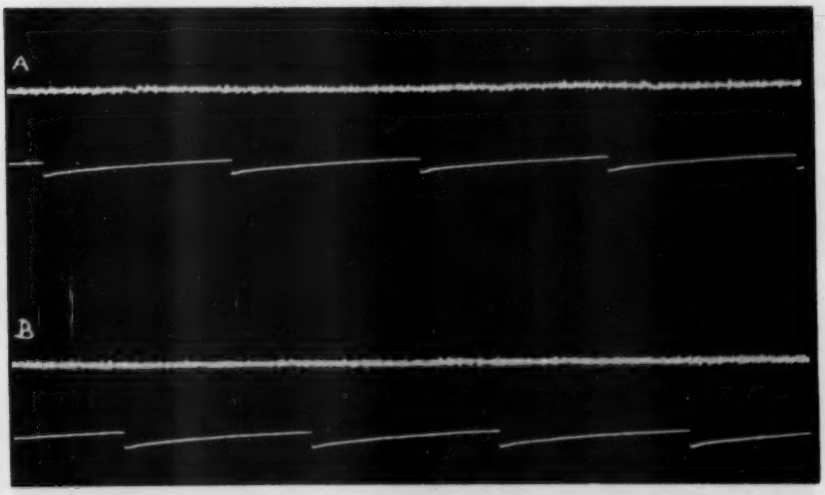
Fig. 10.—Haploscope vergence. Right lateral rectus, upper trace; integrator, lower trace. Asymmetric divergence. O. D. stationary. *A*, start; *B*, end (no change).

All tests give similar results and confirm the thesis that an eye which does not move experiences no significant change in the levels of innervation of its horizontal recti muscles. This must not be interpreted as a monocular dissociation but is a reflection of the central adjustment of version and vergence movements.

D. Lens Vergence (Accommodative)

We may evaluate the interplay of accommodative and fusional vergence by interposing lenses while the subject binocularly views fusion targets. On the major amblyoscope, when concave lenses are interposed accommodative convergence is necessitated (Fig 12); convex lenses inhibit accommo-

Fig. 11.—Haploscope vergence. Right lateral rectus, upper trace; integrator, lower trace. O. S. stationary. Asymmetric divergence. *A*, start; *B*, end, increases.



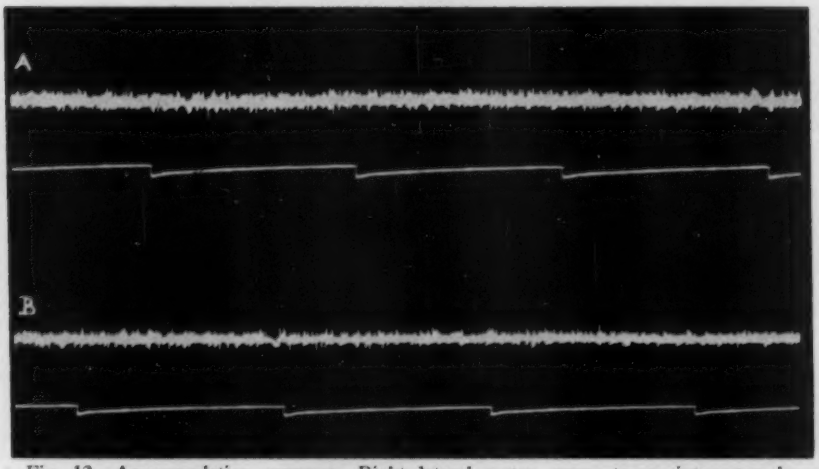


Fig. 12.—Accommodative vergence. Right lateral rectus, upper trace; integrator, lower trace; —2 sphere before O. S. *A*, before; *B*, after, decreased as eye converged.

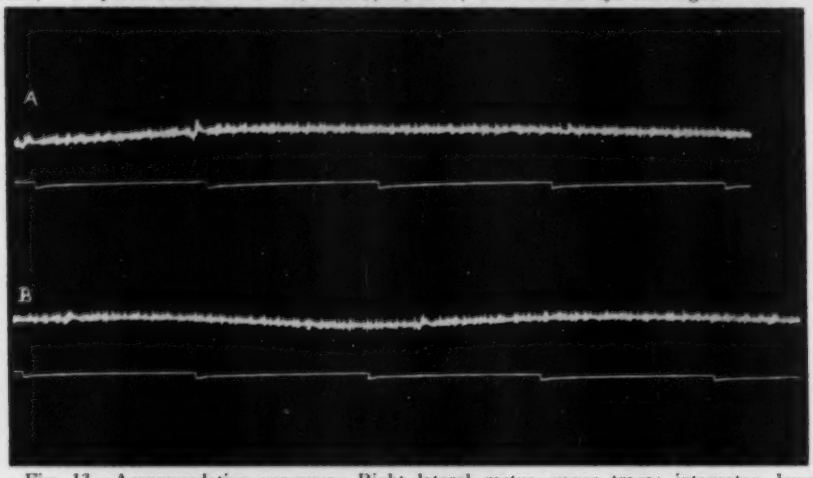
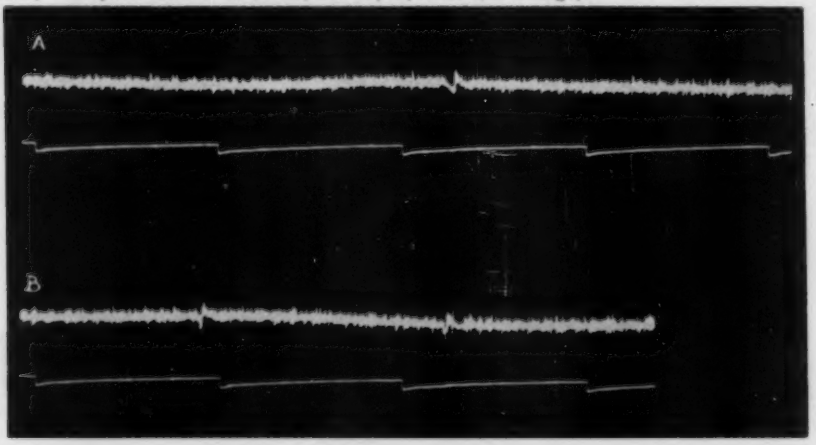


Fig. 13.—Accommodative vergence. Right lateral rectus, upper trace; integrator, lower trace; —2 sphere O. U. *A*, before; *B*, after (no change).

Fig. 14.—Accommodative vergence. Right lateral rectus, upper trace; integrator, lower trace; —2 sphere before O. D. *A*, before; *B*, after (no change).



dative convergence. So long as both eyes are fixing, within the limits of the relative fusional divergence, increments of concave lens power produce no change of innervation to the horizontal recti of either eye (Figs. 13 and 14). At the moment when relative fusional divergence is exceeded, one eye swings in, with the appropriate alterations of its innervation. Up to this point the increasing increments of accommodative convergence were neutralized by equal increments of fusional divergence. Thus, no change was apparent in the levels of innervation of the horizontal muscles. During the addition of minus lenses, if one tube was darkened or the eye was covered that eye immediately swung in, revealing the underlying accommodative convergence no longer neutralized by the fusional divergence (Fig. 12).

Conclusion

It is of considerable importance to realize that all studies confirm the general principle that the outflow of innervation into the motor nerves of the extraocular muscles expresses the centrally adjusted innervation of opposing forces. Normally, cocontraction of antagonistic muscles does not occur; increased innervation of a medial rectus is never counterbalanced by an equivalent increase in the antagonist lateral rectus.

An important corollary of these data is the fact that the training of relative fusional vergence by lenses cannot build greater muscle power. The increase of such fusional amplitudes is necessarily a central phenomenon. It is probable that this also applies to ordinary fusion training. It should be remembered that only a moving eye experiences a peripheral innervational change.

The forces determining the binocular position may be summed up as follows: The innervation-free anatomic position (established under general anesthesia) is modified by tonic innervation, accommodation, fusion, the proximity factor, and fixation. Each of these can be removed by suitable measures, and all are not necessarily present at any given moment. Opposing forces do not exert a tug of war in a struggle for supremacy but are integrated in the brain, the vector resultant emerging in the final common path as a simple reciprocity mechanism.

Summary

Analysis of the interplay of accommodative vergence, fusional vergence, and the effects of lenses in normal subjects has revealed a basic uniformity in the motor response of the extraocular muscles. This consists in the outflow of a vector resultant of innervation produced by central adjustment of all forms of vergence and version innervation. The final common path is expressed as a clear-cut reciprocity mechanism in which cocontraction play no part.

Fusional divergence is an active process.

Fusion training is a central phenomenon, which does not result in greater muscle power.

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Effects of Iodoacetic Acid on Ocular Inflammatory Responses

SYNG-MIN HONG, M.D.; PAUL A. CIBIS, M.D., and MARGUERITE CONSTANT, Ph.D., St. Louis

Introduction

In a previous study [1] evidence was produced that systemic administration of iodoacetic acid (IAA) and ionizing radiation, when administered to the eye only, elicit very similar ocular lesions. The clinical and histological changes produced by these two different agents in the lens and retina of rabbits correlate surprisingly well. However, there were some significant differences observed with regard to the latent periods of the exudative changes in the aqueous humor and vitreous (Table 1). The exudation appeared somewhat earlier after irradiation than after IAA. The most puzzling feature, however, was presented by the fact that the leading cell type in the exudate of irradiated eyes consisted of polymorphonucleocytes, whereas the exudate in the eyes of IAA-treated animals was dominated by red blood cells. Such a difference in the exudative manifestations was difficult to understand and certainly was in contradiction to the commonly favored view that both IAA and ionizing radiation exert their effect by a similar mechanism, i. e., by inhibition of enzymes containing free sulfhydryl groups. Since the white blood cells (WBC) contain such enzymes (Beck,[2] McKinney et al.,[3] Wagner et al.[4,5]), it was suggestive that in the case of IAA, in which the animals were affected systemically, the carbohydrate metabolism was inhibited in all WBC of the body, with the consequent result of a general impairment of their activity. To support such a concept the present study has been undertaken.

TABLE 1.—*Comparison of IAA*- and X-Ray†-Induced Changes in Aqueous and Vitreous of Rabbits*

		Latent Period	
Tissue	Pathologic Changes	IAA	X-Rays
Aqueous	Serous exudation	2 days	6 hr.
	Cellular exudation	2 days	6 hr.
Vitreous	Cellular exudation	4 days	2-4 days

* Intravenous injection of 40 mg. per kilogram of body weight.
† Single dose, 500r to the eye.

Methods

Albino rabbits varying from 1.7 to 2.3 kg. were employed. They were divided into several groups which were subjected to various kinds of trauma to the cornea, as outlined below. As the prime agent of leukotaxic effect, turpentine was used. It was injected into the corneal stroma with a very fine needle in amounts of about 0.02 cc. The solution of sodium iodoacetate used for the intravenous injections into the ear veins of the rabbits had a concentration of 1% and a pH of 7.4. The total doses of sodium iodoacetate given ranged from 30 to 70 mg. per kilogram body weight. In case of local administration of IAA the concentration of the solutions varied from 0.1% to 1%.

The animals were killed at given intervals, as indicated in the tables related to the pertinent experiments. The eyes were enucleated immediately after death, fixated in formalin, sectioned, and stained with hematoxylin and eosin. The histological sections were examined for the presence of leukocytes, edema, necrosis, and disappearance of corneal corpuscles. They were clas-

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TABLE 2.—*Infiltration of the Rabbit Cornea by Leukocytes Following Injury by Turpentine * With and Without Systemic Administration of IAA*

Time of Killing, Hr.	With I. V. Administration of IAA		Without Administration of IAA	
	Eyes, No.	Degree of Infiltration †	Eyes, No.	Degree of Infiltration †
1-4			5	—
5			1	±
6	10‡	—	1	+
9	4§	—	1	+
12	4‖	—	1	+
24	4¶	—	3	+
24	4¶	±	10	++
24	2¶	+		
	28	± to + in 27% of eyes	22	± to ++ in 77% of eyes

* Dose of 0.02 cc. injected into corneal stroma.
† —, no infiltration (Fig. 1); ±, slight infiltration (Fig. 2); +, moderate infiltration (Fig. 3); ++, marked infiltration (Figs. 4 and 5).
‡ Animals received a second injection of IAA of 10 mg. per kilogram three hours later; total dose, 40 mg. per kilogram.
§ Animals received a second injection of IAA of 20 mg. per kilogram three hours later; total dose, 50 mg. per kilogram.
‖ Animals received a second injection of IAA of 20 mg. per kilogram three hours later and a third, six hours later. Total dose, 70 mg. per kilogram.
¶ Dose of IAA given was 30 mg. per kilogram of body weight.

sified with regard to the degree of leukocytic infiltration as indicated by the footnote to Table 2 and the legends of Figures 1 to 4.

Experiments and Results

EXPERIMENT 1.—Experiment 1 was conducted to determine whether the systemic administration of IAA would prevent the migration of leukocytes into the cornea injured by turpentine. The data in Table 2 show that following intrastromal injection of turpentine a cellular infiltration of the cornea of the control animals was apparent within five hours. The migration of the leukocytes occurred preferably in the interlamellar spaces of the anterior third of the corneal stroma, as shown in Figures 3 and 4. The degree of leukocytic infiltration increased with time and was, in general, significantly greater at the limbal side of the corneal wounds than in the center. The density of the infiltration was usually the greater the thicker the layer of corneal stroma involved. The area of turpentine injection showed a decreased number of corneal corpuscles and signs of severe damage of the stroma in form of pallor and swelling. The leukocytic infiltration comprised the entire thickness of the cornea at the limbal side of the injury in the severest cases (Fig. 5). In the 16 animals with intravenous administration of IAA (30 to 70 mg. per kilogram body weight) and injury of the cornea by turpentine, the migration of the leukocytes into the corneal stroma could be delayed for over a period of 24 hours. If a single dose of IAA (30 mg. per kilogram) was given, leukocytic infiltration of the cornea was observed in more than 50% of the animals prior to 24 hours. However, the degree of infiltration in these cases

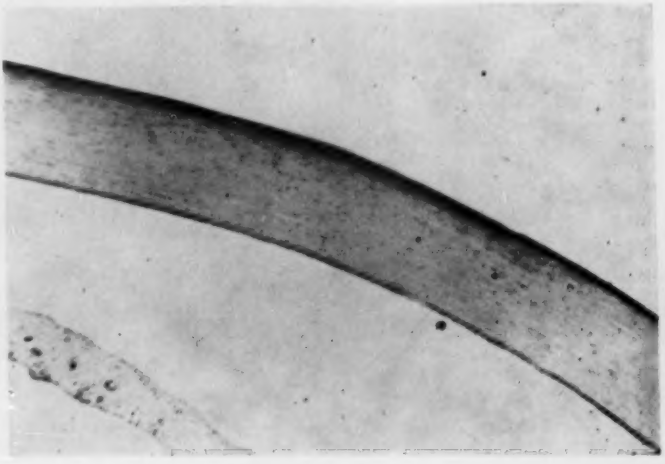

Fig. 1. — Histological section of normal rabbit cornea. Absence of leukocytic infiltration (—). Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

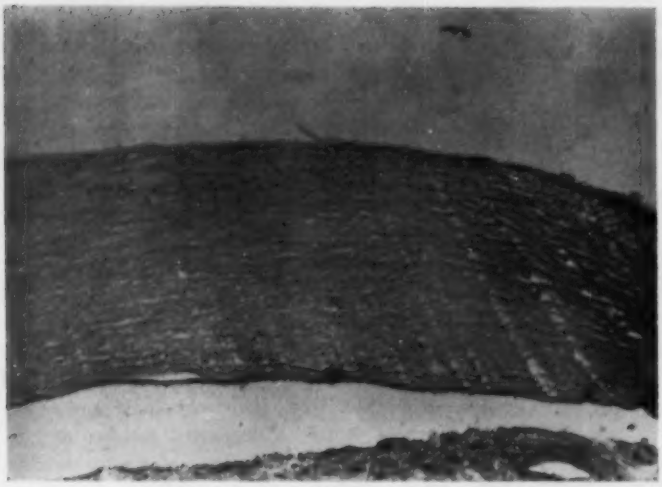

Fig. 2.—Slight leukocytic infiltration (±) of rabbit cornea, nine hours after intrastromal injection of 0.02 cc. turpentine (at left). Moderate swelling of stroma and desquamation of epithelium. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

appeared to be much less than in the animals injured by turpentine without systemic administration of IAA. Three of the seven animals with a single dose of IAA did not show any migratory activity at all within the 24 hours of observation. Whenever leukocytic infiltration in the cornea was observed, the endothelium was found affected in form of swelling, cellular deposits at the posterior surface of the cornea, and, sometimes, desquamation.

The result of the first experiment may be summarized as follows: Of the 28 eyes of 16 animals subjected to systemic administration of IAA, 27% showed a mild to medium degree of leukocytic infiltration within 24 hours; whereas, in the 20 eyes of 18 animals injured by turpentine without systemic IAA, 77% developed a mild to severe degree of leukocytic infiltration. The inhibitory effect of systemic administration of IAA upon the migration of leukocytes into the cornea injured by turpentine is illustrated by Figures 6 and 7.

Experiments 2 and 3.—These experiments were conducted to determine whether

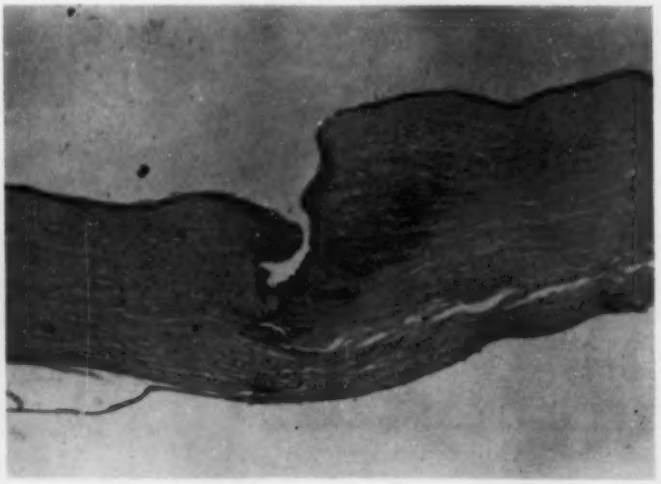

Fig. 3.—Moderate leukocytic infiltration (+) of rabbit cornea, 12 hours after intrastromal injection of 0.02 cc. turpentine. Note deep corneal wound at site of injection (at left), accumulation of leukocytes, and swelling preferentially at limbal side (at right). Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

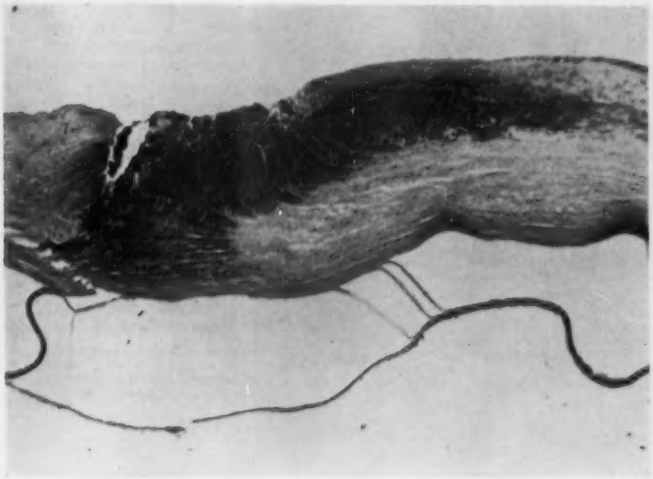

Fig. 4.—Marked leukocytic infiltration (++) of rabbit cornea, 24 hours after intrastromal injection of 0.02 cc. turpentine (at left). Descemet's membrane and endothelium artificially detached. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

local administration of IAA effects the cellular infiltration of the turpentine-injured cornea by leukocytes. In Experiment 2 the right eyes of six rabbits were subjected to subconjunctival injections of 0.1% to 1.0% solutions of IAA around the limbus, as indicated in Table 3. The left eyes of the same animals were also treated with turpentine, without the perilimbal injection of IAA, however. All animals were killed after 24 hours. The results of these experiments indicate that subconjunctival injections of IAA did not prevent the migration of leukocytes to the area injured by turpentine. There was no significant difference between the IAA-injected and the control eyes.

In Experiment 3, IAA, 0.02 cc. of a 0.5% solution, was injected into the stroma of the right eyes of 12 rabbits. The left eyes of the same animals received an intrastromal injection of physiological saline solution in equivalent amount. No turpentine was used in this group of animals.

The illustrations in Figures 8 and 9 and the data in Table 4 indicate that IAA itself, when injected into the corneal stroma, can

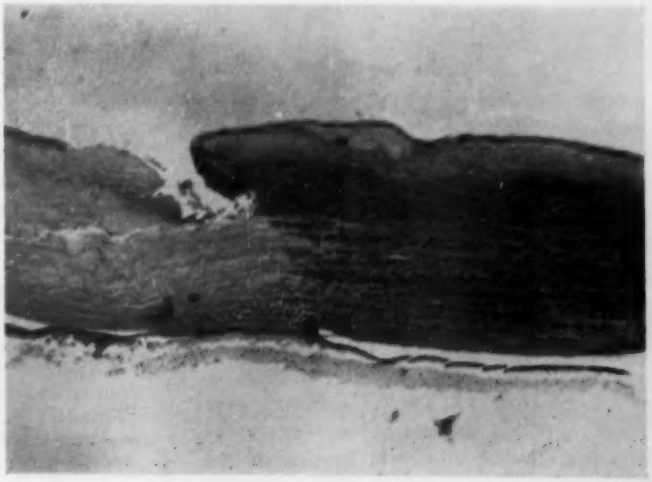

Fig. 5.—As Figure 4, but whole thickness of cornea involved at limbal side. Protein precipitation and leukocytic deposits at posterior surface of cornea. Area of subepithelial edema to the right of wound. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

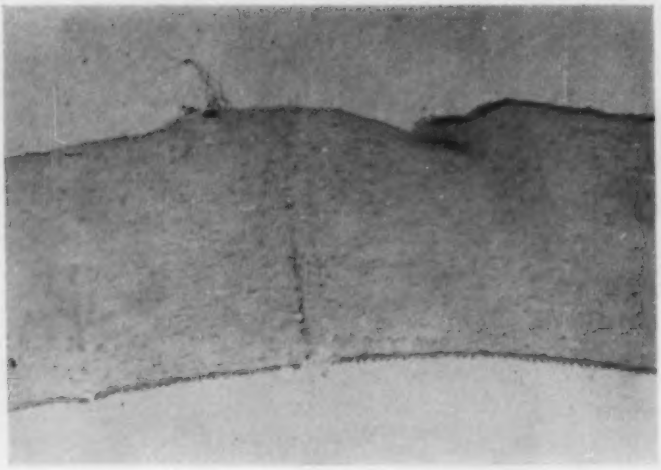

Fig. 6.—Section of cornea 12 hours after turpentine injection of rabbit treated with intravenous injection of IAA (70 mg. per kilogram). Note absence of leukocytes. Desquamation of epithelium over area of injection (at left). Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

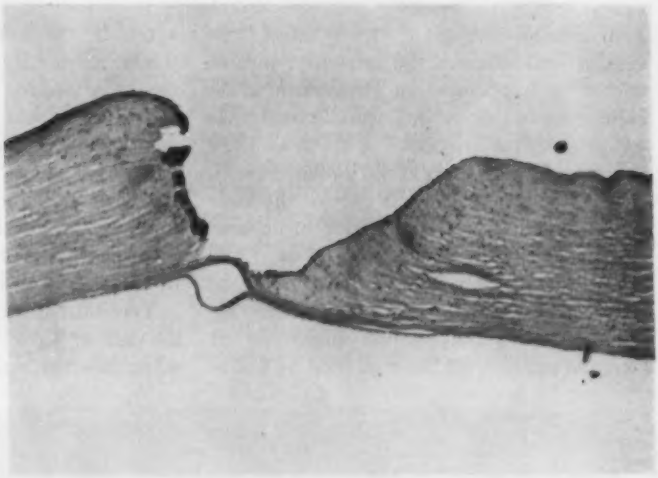

Fig. 7.—Large corneal defect, 24 hours after turpentine injection into stroma. Intravenous injection of 30 mg. IAA per kilogram of body weight prevented leukocytic infiltration to traumatized cornea. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

produce a mild leukocytic reaction which develops after 24 hours. This reaction to IAA was associated with epithelial and stromal swelling of the entire cornea which lasted from 60 to 72 hours. Denudation of the epithelium was observed in a few cases. The endothelium did not appear affected significantly. No leukocytic infiltration was observed in the control eyes, which had been subjected to injections of physiological saline.

EXPERIMENT 4.—Two experiments were conducted to determine the effect of steroids on the cellular infiltration of the cornea following injury by turpentine injection to both eyes. In the first group 10 animals were employed, the right eyes of which were treated with Metimyd * applied every two hours over a period of eight hours following the injection of turpentine. The left eyes, also injured by turpentine, served as controls. The animals were killed as indicated in Table 5. Leukocytic infiltration was found to take place in either eye after six

* Commercial preparation of Schering Corporation, Bloomfield, N. J., containing 5 mg. of prednisolone acetate and 100 mg. of sulfacetamide sodium per cubic centimeter.

TABLE 3.—*Migration of Leukocytes into the Cornea Injured by Turpentine* With and Without Perilimbal Injection of IAA†*

Rabbits, No.	With Perilimbal Injection of IAA (One Eye)		Without Injection of IAA (Other Eye)
	Dose of IAA, Mg.	Degree of Infiltration	Degree of Infiltration
1	2	+	+
1	10	+	+
2	20	+	+
1	20	+	±
1	20	±	++

* Intrastromal injection of 0.02 cc.
† Dose, 2 cc. of 0.1% to 1% solution. All animals were killed after 24 hours following the corneal injury with turpentine. For further explanation see Table 2.

hours. There was some noticeable difference with regard to the degree of infiltration insofar as the eye additionally treated with Metimyd showed less reaction.

In the second group of Experiment 4, ten albino rabbits received 25 mg. of cortisone acetate (Cortone) intramuscularly in addition to the local application of Metimyd as outlined above. Both eyes were injured by intrastromal injection of turpentine. The results of this series of the experiment are shown in Table 6. They indicate that leukocytic infiltration occurred in the cornea of both eyes at about the same time, but it was

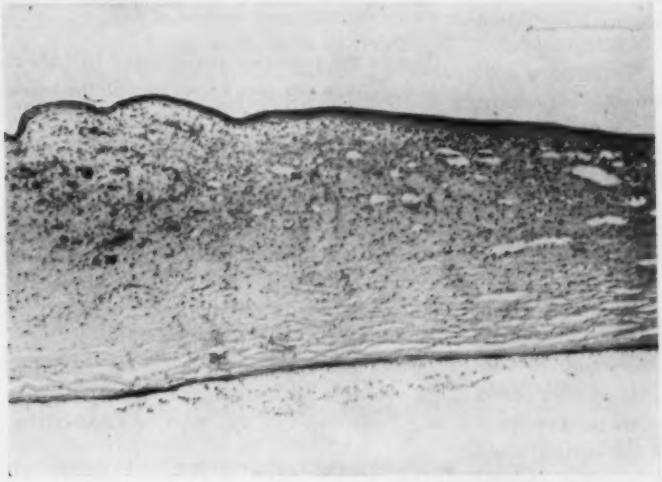

Fig. 8. — Histological section of rabbit cornea, nine days after intrastromal injection of IAA (0.02 cc. of 0.1% solution). Diffuse leukocytic infiltration of moderate degree, neovascularization, and leukocytic cell deposits. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

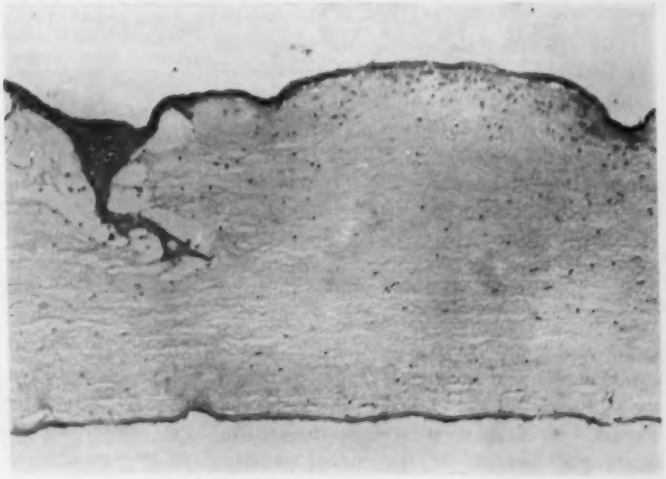

Fig. 9.—Mild leukocytic infiltration of cornea, nine days after intrastromal injection of IAA (0.02 cc. of 0.1% solution). Excessive stromal edema around epithelial proliferation at site of injection. Formalin, hematoxylin and eosin; reduced about ¼ from mag. × 44.

TABLE 4.—*Leukocytic Infiltration of the Cornea Following Intrastromal Injection of IAA* (O. D.) as Compared with Physiological Saline Solution (O. S.)*

Time of Killing	Rabbits, No.	Degree of Leukocytic Infiltration	
		O. D. (IAA)	O. S. (NaCl)
1 day	2	±	—
2 days	2	+	—
4 days	2	+	—
1 wk.	2	+	—
2 wk.	2	+	—
1-14 days	10	± to +	—

* Dose, 0.02 cc. of a 0.5% solution.

somewhat less in degree than in eyes injured by turpentine without additional treatment of any kind.

Comment

The results of our experiments with turpentine as leukotaxic agent applied to the cornea are in full agreement with the observations of Cohnheim,[6] Senftleben,[7] and Leber.[8] In his classical monograph [8] Leber also mentions the fact that injections of turpentine into the anterior chamber result in death of all fixed corneal corpuscles and that heavy leukocytic infiltrations develop in the corneal stroma with sparing of a centrally located area of necrosis. The sparing of the central area of the cornea could also be observed consistently in our experiments with turpentine (Figs. 3 to 5).

The question concerning the origin of the leukocytes in the cornea of turpentine-injured eyes has already been settled by Cohnheim [6] and Senftleben.[7] These authors proved to the satisfaction of Leber, who had repeated their experiments with many other agents, that the leukocytes around the chemically necrotized area in the cornea were not derived from the fixed corneal corpuscles by proliferation but originated from the conjunctival vessels by migration. Leber also mentioned the fact that the leukocytes were more frequently found between the lamellae of the anterior third of the stroma, i. e., in the level corresponding to the anatomical location of the limbal vessels,

TABLE 5.—*The Effect of Turpentine* upon the Migration of Leukocytes into the Cornea With (O. D.) and Without (O. S.) Local Administration of Steroid†*

Time of Killing, Hr.	Rabbits, No.	Degree of Infiltration	
		O. D.	O. S.
6	1	±	+
	1	+	+
9	1	+	+
12	1	+	+
	1	±	+
18	1	+	++
24	1	±	++
	1	++	++
48	2	+	++

* Intrastromal injection of 0.02 cc.
† Prednisolone acetate, 5 mg., and sulfacetamide sodium, 100 mg. per cubic centimeter (Metimyd Ophthalmic Solution) instilled into O. D. every two hours.

than in the posterior two-thirds. In Leber's as well as in our own experiments, the leukocytes were observed to change the direction of migration toward the deeper layers of the cornea in the vicinity of the central area of necrosis (Figs. 3 and 4). There, the cells accumulated in all layers, forming a ring-shaped zone of infiltration around the lesion produced by turpentine. The clinical and histological picture of the severer cases presented itself as that of a ring abscess.

Since all these changes can be inhibited by systemic administration of IAA, one might surmise that the reactive mobilization

TABLE 6.—*The Effect of Intramuscular Administration of Steroids* on the Cornea Injured by Intrastromal Injection of Turpentine† With (O. D.) and Without (O. S.) Topical Administration of a Steroid‡*

Time of Killing, Hr.	Rabbits, No.	Degree of Leukocytic Infiltration	
		O. D. (Metimyd)	O. S. (Control)
6	1	±	+
	1	+	±
9	1	+	+
12	1	+	±
	1	+	+
18	1	+	+
24	1	+	+
	1	++	++
48	2	++	++
6 to 48	10	± to ++	± to ++

* Cortisone, 25 mg. per animal given just prior to turpentine.
† Dose, 0.02 cc. of turpentine.
‡ Metimyd.

of the leukocytic defense forces in the body are depressed by inhibition of their energy production. No decrease of WBC was noticed in the blood counts. It appears less likely that the absence of the leukocytic infiltration in the turpentine-injured cornea is the result of some repelling mechanism because of changes induced in the cornea by IAA itself; for neither a subconjunctival injection of IAA around the limbus nor one into the stroma did prevent the leukocytic migration. From this observation one might infer a direct effect of IAA on the leukocytes in the blood. If this is the case, such a mechanism would supply a plausible explanation of the controversial observation which initiated this study—namely, erythrocytes prevail in the exudate of the anterior chamber after the intravenous injection of IAA, whereas the leukocytes predominate in the exudate produced by ionizing radiation.

Our experiments with local application of steroids did not provide conclusive data. The differences observed with local application were too small to be statistically significant. However, the plain fact that the systemic and local application of steroid did not prevent the leukocytic infiltration in any case indicates that the inhibition of migration into the turpentine-injured cornea by IAA is not indicative of an indirect effect brought about by formation of cortisone.

The inhibition of leukocyte migration into the turpentine-injured cornea by intravenous injection of IAA is not specific for this part of the body, for it could also be demonstrated quantitatively in the skin.

At this point it may be timely to make some comments about the corneal epithelium in the area of IAA injection (Fig. 9). The corneal epithelium proliferated over the wound afflicted by the needle. This proliferation occurred within 24 to 48 hours in spite of severe damage to the stroma, as indicated by tremendous swelling, vacuole formation around the proliferated epithelium, and rarification of the corneal corpuscles as a result of impaired carbohydrate metabolism, as has been demonstrated by Parnas,[9] Mackworth,[10] and Herrmann et al.[11]

The actual mechanism by means of which IAA exerts its effect on the tissue metabolism is not completely understood, since it seems not to be restricted to the thiol-enzymes alone (Barron [12]).

Summary

Inhibition of leukocytic infiltration into the turpentine-injured cornea was achieved in rabbits by intravenous injection of a 1% solution of iodoacetic acid (IAA) varying in dose from 30 to 70 mg. per kilogram of body weight.

Subconjunctival injections of a 0.1% to 1% solution of the sodium salt of IAA around the limbus did not prevent the migration of leukocytes into the turpentine-injured cornea.

The histological changes following an intrastromal injection of a 0.5% solution of sodium iodoacetate are described and discussed.

Local as well as systemic administration of steroids was not as effective as IAA in preventing the development of a leukocytic infiltration in the turpentine-injured cornea.

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Further Studies on the Use of Digital Pressure in Cataract Surgery

I. Optimal Length of Time for Application of Digital Pressure

RALPH E. KIRSCH, M.D., Miami, Fla.

In a previous communication[1] it was shown that application of five minutes of digital pressure after the retrobulbar injection, following the ideas of Atkinson[2-5] and Chandler,[6] constitutes a very definite clinical safeguard against the loss of vitreous during cataract surgery. It was further shown that, thus far, the best experimental criterion for judging this safeguarding action of digital pressure lay in the depth and duration of the accompanying ocular hypotony. It has accordingly now become desirable to determine the optimal length of time for application of digital pressure; for, in an operation already considerably lengthened by the use of modern corneoscleral suture techniques, it becomes important to know if the same safety may be achieved in less than five minutes or, conversely, if even greater safety is induced by more than five minutes of digital pressure.

Materials and Methods

The material for this study consisted of 60 eyes studied during cataract operation performed by me in the manner described in the previous communication.[1] The methods employed consisted essentially of the measurement, in the operating room during the actual cataract surgery following the retrobulbar injection, of the intraocular pressure before, during, and after the application of digital pressure of from 1 to 10 minutes' duration. Where the factor of duration of hypotony was under consideration, a retrobulbar injection followed by digital pressure of varying lengths of time was performed on the eye not operated on and measurement of the hypotony was continued at two-minute intervals by an assistant while the surgeon proceeded with the lens extraction in the eye being operated upon.

Inasmuch as the original study was begun prior to the adoption of the 1954 calibration scale for Schiøtz tonometry, for the sake of ease of comparison the old Schiøtz scale has been used throughout these studies.

Initially the ocular tension was recorded at one-minute intervals during the application of digital pressure. The tension was first measured in a group of cases in which a total of two and one-half minutes of digital pressure was applied, then in groups of five minutes and seven and one-half minutes of digital pressure. Finally, the intraocular pressure was measured at 2½-minute intervals in a group of cases of 7½ minutes' duration of digital pressure and in a group of 10 minutes' duration. In each of these series observations were made upon the duration of the hypotony in the fellow eye (not operated on) subjected to the same retrobulbar injection and digital pressure as the eye operated on.

The anesthetic solution used in this study for akinesia and retrobulbar injection was 2% lidocaine (Xylocaine) hydrochloride with epinephrine and hyaluronidase.

In the Tables, recognizing the inaccuracy of tonometer readings in very hypotonic eyes, in those cases where the calibrated

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From the Department of Ophthalmology, Mt. Sinai Hospital of Greater Miami, and the Division of Ophthalmology, University of Miami School of Medicine.

TABLE 1.—*Minute-by-Minute Measurement of Intraocular Pressure (Schiotz)—Two and One-Half Minutes' Duration*

Case	Initial IOP	Postretro. IOP	IOP During Digital Pressure			Minutes IOP Remained Below 10 Mm.
			1 Min.	2 Min.	2½ Min.	
1	20.1	16.9	10.0	8.0	9.0	1
2	16.9	11.9	2.0	2.0	0 (14)	
3	16.9	13.2	4.0	4.0	1.0	8
4	18.5	9.0	3.0	1.0	2.0	
5	21.8	20.1	16.9	13.2	11.9	
6	13.2	14.2	14.2	11.9	10.0	
7	15.6	16.9	11.9	9.0	9.0	2
8	16.9	20.1	18.5	18.5	13.2	
9	20.1	21.8	23.4	20.1	20.1	
10	21.8	21.8	18.5	13.2	10.0	
Average		16.6	12.2	10.1	8.6	

reading approaches zero the actual scale reading on the tonometer is inserted in parenthesis. This furnishes at least a method of comparing relative hypotony.

Results

Tables 1, 2, and 3 summarize the results upon the intraocular pressure of the minute-by-minute application of digital pressure after the retrobulbar injection. Table 1 documents those instances in which digital pressure was applied for two and one-half minutes; Table 2 those cases wherein digital pressure was applied for five minutes, and Table 3, for seven and one-half minutes. Tables 4 and 5 represent cases wherein the minute-by-minute measurement was replaced by measurement of the tension every 2½ minutes for durations of 7½ minutes (Table 4) and 10 minutes (Table 5).

Table 1 reveals at once that application of only two and one-half minutes of digital pressure does not, in the majority of cases, produce a hypotony of the depth and duration that can be achieved by somewhat longer application of pressure. It is to be noted, however, that in an occasional case a deep and lasting hypotony is produced, but this is not sufficiently consistent to warrant recommending the reduction of time of application of digital pressure in the operating room to two and one-half minutes.

With increase of the length of digital pressure to five minutes we see (Table 2) that there is a significant increase in the hypotony produced. Figure 1A summarizes the data in graphic form, and Figure 1B plots the mean of the data in the 13 cases of five minutes of minute-by-minute testing. It is seen that the greatest decrease in ocular tension occurs in the first minute of digital pressure but that there is relatively steady decline throughout the remaining four minutes. From the clinical experience with the safeguarding action of five minutes of digital pressure reported in the previous communication,[1] it would appear that this is an adequate amount of

TABLE 2.—*Minute-by-Minute Measurement of Intraocular Pressure—Five Minutes' Duration*

Case	Initial IOP	Postretro. IOP	IOP During Digital Pressure					Minutes IOP Remained Below 10 Mm.
			1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	
11	18.5	11.9	4.0	4.0	3.0	0 (16)	0 (16)	
12	18.5	13.2	1.0	0 (15)	0 (17)	0 (17)	0 (17)	
13	16.9	11.9	6.2	6.2	6.2	5.0	2.0	
14	18.5	13.2	0 (17)	0 (18)	0 (19)	0 (20)	0 (21)	
15	18.5	15.6	3.0	0 (15)	0 (15)	0 (16)	0 (15)	
16	15.6	10.0	8.0	4.0	0 (14)	0 (18)	0 (18)	
17	18.5	16.9	14.0	11.0	6.2	6.2	4.0	
18	18.5	13.2	10.0	11.0	9.0	8.0	8.0	
19	14.2	14.2	12.0	10.0	8.0	6.0	3.0	11
20	16.9	16.9	16.0	14.0	13.0	10.0	10.0	
21	15.6	13.2	11.0	9.0	8.0	6.2	5.0	
22	16.9	14.2	11.9	8.0	4.0	4.0	4.0	
23	18.5	10.0	3.0	1.0	2.0	2.0	0 (16)	
Average		13.4	7.7	6.0	4.6	3.6	2.8	

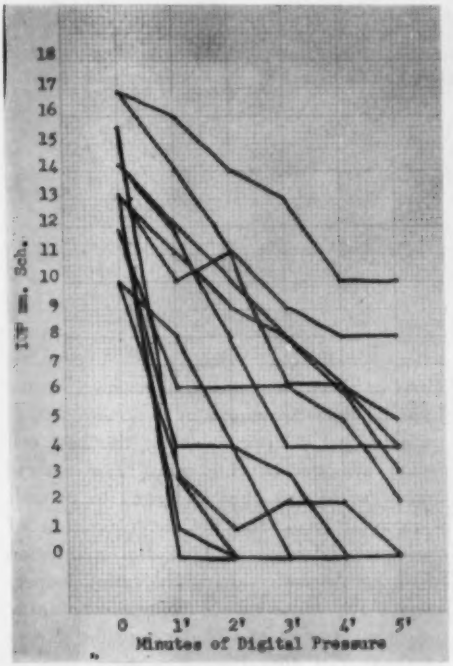

Fig. 1A.—Graph of Table 2. Intraocular pressure after retrobulbar injection.

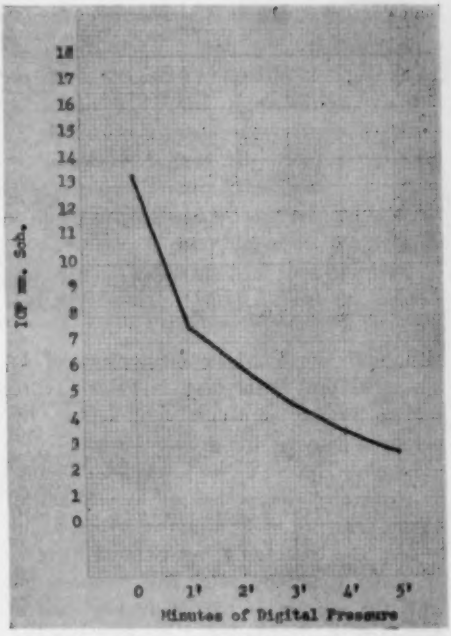

Fig. 1B.—Mean of Table 2. Intraocular pressure after retrobulbar injection.

digital pressure, and the graph in Figure 1B gives us an accurate analysis of the minute-by-minute effect on ocular tension in the average eye. It is of interest to note the close correlation between the final average intraocular pressure in this Table (2.8 mm., Schiøtz), as compared with the final average of 2.3 mm. (Schiøtz) in the 50 cases studied in the operating room in the previous paper,[1] suggesting that the graph in Figure 1B represents a truly typical surgical case subjected to five minutes of digital pressure.

In Tables 3 and 4 are summarized the results of application of seven and one-half minutes of digital pressure, the former employing the minute-by-minute testing method and the latter the measurement at intervals of two and one-half minutes. Here it is seen that beyond five minutes there is a further but more gradual decrease in the ocular ten-

TABLE 3.—*Minute-by-Minute Measurement of Intraocular Pressure—Seven and One-Half Minutes' Duration*

	Initial	Post-retro.	IOP During Digital Pressure																Minutes IOP Remained Below 10 Mm.
Case	IOP	IOP	1 Min.	2 Min.		3 Min.		4 Min.		5 Min.		6 Min.		7 Min.		7½ Min.			
24	23.4	16.9	16.9	10.0		8.0		8.0		6.2		3.0		1.0		0	(14)		
25	16.9	16.9	15.6	13.2		10.0		10.0		10.0		10.0		10.0		9.0			
26	14.2	11.9	11.0	11.0		9.0		10.0		8.0		7.0		4.0		6.2			9
27	15.6	11.9	11.0	8.0		10.0		7.0		6.2		7.0		4.0		6.2			
28	13.2	13.2	7.0	10.0		11.0		0	(14)	4.0		5.0		4.0		5.0			19
29	13.2	20.1	14.2	11.9		10.0		10.0		9.0		8.0		8.0		6.2			
30	14.2	14.2	14.2	11.9		11.9		11.0		10.0		10.0		8.0		5.0			3
31	13.5	14.2	14.2	9.0		9.0		9.0		7.0		2.0		2.0		3.0			
32	15.6	11.9	2.0	0	(15)	0	(17)	0	(15)	0	(19)	0	(20)	0	(20)	0	(21)		
33	18.5	15.6	11.0	11.0		1.0		0	(15)	0	(14)	0	(15)	0	(17)	0	(18)		27
34	15.6	20.1	16.9	16.9		13.2		15.6		10.0		10.0		9.0		6.2			9
35	16.9	11.0	9.0	6.2		0	(14)	0	(15)	0	(15)	0	(17)	0	(17)	0	(18)		
36	18.5	18.5	18.5	10.0		7.0		8.0		7.0		4.0		4.0		2.0			13
Average			15.1	12.4		9.9		7.7		6.8		5.9		5.0		4.1			3.7

TABLE 4.—*Measurement of Intraocular Pressure Every Two and One-Half Minutes—Seven and One-Half Minutes' Duration*

Case	Initial IOP	Postretro. IOP	IOP During Digital Pressure			Minutes IOP Remained Below 10 Mm.
			2½ Min.	5 Min.	7½ Min.	
37	14.2	9.0	2.0	0 (17)	0 (20)	
38	23.4	15.6	4.0	3.0	4.0	
39	10.0	14.2	4.0	(18)	0 (20)	21
40	14.2	14.2	4.0	3.0	3.0	25
41	12.0	5.0	0 (14)	0 (19)	0 (20)	
42	11.0	13.2	10.0	6.2	0 (14)	26
Average		11.8	4.0	2.0	1.1	

sion, with the final average tension of 1.1 mm. (Schiotz) in the cases in Table 4 representing the most profound final average hypotony of any of the groups tested.

Finally, Table 5 outlines the data obtained in extending the period of application of digital pressure to 10 minutes. Here, again, is seen the continuing but gradual increase in ocular hypotony after five minutes, but with the tension at extremely low rate of decline in the last two and one-half minutes.

Figure 2 represents a summary of all of the data by presenting a composite graph derived from the mean of each of the groups of cases outlined in Tables 1 through 5.

Comment

Although it is not known with certainty that measurement of ocular hypotony constitutes an accurate criterion for judging the safeguarding action of digital pressure after retrobulbar injection in preventing vitreous loss in cataract surgery, in the light of data presented in a previous communication,[1] it appears to be the best criterion available at this time. The present investigation was thus designed to provide a rational basis for the determination of the optimal length of time for application of digital pressure during the cataract operation. By a series of minute-by-minute measurements of the ocular tension during application of digital pressure in the operating room, it has been determined that the greatest fall per minute in intraocular pressure occurs in the first minute, that a significant continuing fall occurs between the second and fifth minutes, and that a final shallowing of the curve of decrease in tension occurs approximately at the end of the fifth minute. Moreover, virtually all eyes have had imparted to them at the end of the fifth minute of digital pressure a depth

TABLE 5.—*Measurement of Intraocular Pressure Every Two and One-Half Minutes—Ten Minutes' Duration*

Case	Initial IOP	Post-retro. IOP	IOP Dur ng Digital Pressure				Minutes IOP Remained Below 10 Mm.
			2½ Min.	5 Min.	7½ Min.	10 Min.	
43	11.0	14.2	2.0	0 (14)	0 (17)	0 (15)	
44	10.0	13.2	0 (14)	0 (17)	0 (17)	0 (20)	11
45	20.1	11.9	10.0	3.0	4.0	0 (14)	
46	18.5	11.0	0 (14)	3.0	0 (19)	0 (19)	
47	20.1	20.1	18.5	20.1	18.5	10.0	19
48	25.4	11.0	10.0	5.0	0 (15)	0 (15)	
49	20.1	8.0	10.0	6.2	2.0	4.0	
50	21.8	21.8	10.0	0 (14)	0 (15)	0 (19)	
51	23.4	20.1	11.9	8.0	6.2	4.0	
52	23.4	23.4	13.2	10.0	8.0	8.0	3
53	13.2	20.1	11.9	1.0	0 (15)	0 (19)	
54	18.5	18.5	10.0	6.2	4.0	0 (14)	
55	15.6	7.0	5.0	1.0	0 (15)	0 (15)	
56	10.0	10.0	6.2	1.0	0 (15)	0 (18)	13
57	11.9	10.0	0 (14)	6.2	0 (14)	0 (14)	28
58	14.2	8.0	0 (14)	0 (14)	0 (18)	0 (20)	
59	16.9	16.9	11.0	3.0	0 (19)	0 (20)	
60	20.1	10.0	10.0	0 (14)	0 (15)	0 (16)	24
Average		14.1	7.7	4.1	2.4	1.3	

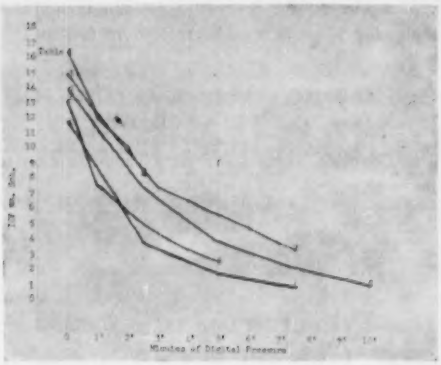

Fig. 2.—Composite graph of Tables 1 to 5. Intraocular pressure after retrobulbar injection.

and duration of hypotony that has been found to be clinically safe.

Evidence is presented that continuation of application of digital pressure beyond five minutes is associated with a further but very gradual decrease in ocular tension, indicating that the longer the digital pressure is applied the greater is the hypotony produced.

It may be of comfort to the surgeon when operating upon an exceptional case wherein the anticipation of vitreous loss is greater than usual (the bulging eye; the short, thick-necked patient; the asthmatic patient; the coughing patient, or the unruly patient) to know that some little extra safety may be induced by increasing the duration of digital pressure to 7½ minutes or even to 10 minutes. It is believed, however, that the data presented here warrant the conclusion that the application of five minutes of digital pressure constitutes the optimal duration of application.

As for duration of hypotony, it is seen that, although there is an increase in the duration of an intraocular pressure under 10 mm. (Schiøtz) with the longer applications of digital pressure, the data of the previous [1] and present communications indicate that such long duration of hypotony does not appear of practical value. There is apparently no advantage in retaining deep hypotony after the lens has been extracted and the corneoscleral sutures have been tied. Here, again, it is indicated that five minutes constitutes the optimal time for application of digital pressure in cataract operations.

Finally, it will be of more than passing interest to every cataract surgeon to study the graph in Figure 1B, for it provides a clear demonstration of the changes in intraocular pressure which occur in the average case of cataract operation when the surgeon utilizes the application of five minutes of digital pressure.

Summary

Evidence is adduced concerning the optimal length of time for application of digital pressure by frequent measurement (minute-by-minute or every two and one-half minutes) of the ocular tension concomitant with the application of digital pressure following retrobulbar injection during cataract surgery.

Digital pressure was applied for 2½ minutes, 5 minutes, 7½ minutes, and 10 minutes.

The greatest fall per minute in intraocular pressure occurs in the first minute of application of digital pressure. A significant continuing fall occurs between the end of the first and fifth minutes. A final shallowing of the curve of decrease in tension occurs approximately at the end of the fifth minute. Between the fifth and tenth minutes only a slight further decrease in ocular tension occurs.

It is concluded that the optimal length of time for application of digital pressure following the retrobulbar injection in cataract surgery is 5 minutes.

Figure 1B provides the ophthalmic surgeon with a graphic summary of the intraocular pressure changes occurring minute-by-minute in his application of five minutes of digital pressure during cataract surgery.

The operating room personnel of the Mt. Sinai Hospital of Greater Miami cooperated in this investigation.

1345 N. Bayshore Dr. (32).

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Radiation Effect on Intraocular Tissues in Radon Seed Treatment of Retinoblastoma

EDWARD TAMLER, M.D.; FRANK C. WINTER, M.D., and PAUL TOCH, M.D., San Francisco

For some time now, ophthalmologists have been attempting to save the less involved eye in bilateral retinoblastoma with radiation therapy. The results with x-ray therapy alone have generally been disappointing. Although retinoblastoma is radiosensitive, the dose lethal to the tumor approaches the tolerance of normal structures in the posterior part of the eye and exceeds the tolerance of the structures of the anterior part of the eye.[1] The relatively narrow margin between the cancericidal dose and the dose tolerated by normal ocular tissues has given rise to many complications with x-ray therapy.[2] The complication of gravest concern is late vitreous hemorrhage from damaged retinal blood vessels.[3] In order to reduce the incidence of complications, the dosage of x-ray has been decreased by employing along with it a radiomimetic drug, such as the nitrogen mustards [4] or, especially, triethylene melamine (TEM).[3] The results of this combined therapy await final evaluation.

Another method which has been tried in order to avoid the major complications of x-ray treatment is the use of radon seeds. Presumably the application of the seeds close to the neoplasm concentrates the radiation in the tumor area and thereby causes less destruction to other ocular and extraocular tissues. Combined use of radon seeds and x-ray irradiation allows for smaller doses of the latter. Stallard has been the major proponent of the use of radon seeds and has reported extensively on their use in the treatment of retinoblastoma.[5-10] At first the seeds were inserted directly into the tumor tissue,[5] but this technique was found to be very damaging to surrounding tissues and was discarded in favor of suturing the seeds to the sclera.[6] From seeds originally of 3 to 5 mc. in strength,[5] Stallard changed to seeds of 1 to 2 mc.[8] He states that a dose of 0.7 mc. will destroy a surrounding area of 1.5 mm. in radius; 2 mc. will destroy an area of 3.5 mm. radius. He noted shrinking of the tumor in the second or third week after implantation.[8] Though he obtained good results in 60% of his cases, complications such as cataract, retinal exudates, hemorrhage, and retinal detachment occurred.[8] He believes that some retinoblastomas are more radiosensitive than others and that the dose of radiation is still empirical.[9] He feels that he has gotten fewer complications with radon seeds than others have gotten with deep x-rays.[9] More recently, Stallard has been using discs containing radium or radioactive cobalt to treat retinoblastomas, this technique allowing for evener or more uniform irradiation.[9]

Very little is known generally about the effect of specific doses of radiation on human intraocular tissues. There have been few histological reports of the effect of radiation on such tissues in the treatment of retinoblastoma. Stallard made a pathological study of eight eyes containing irradiated retinoblastoma,[9] but he does not tell exactly how they were irradiated nor does he attempt to relate dosage to the histological changes observed. He describes atrophy and avascularity of the retina and choroid in and around the irradiated area. Irradiated cells

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From the Division of Ophthalmology, Department of Surgery (Drs. Tamler and Winter) and Department of Radiology (Dr. Toch), Stanford University School of Medicine.

showed pyknosis and karyorrhexis of their nuclei and atypical mitosis. There were degeneration, disorganization, and atrophy of the irradiated neoplasm. Some specimens showed disappearance of all retinoblastoma cells or calcification of some tumor islands. Others showed clumps and columns of neoplastic cells surviving or persisting in degenerated form, surrounded by attempts at fibrosis. There were edema of the surrounding retina and pigmentary changes in the periphery of the irradiated zone. The ganglion-cell layer was largely replaced by fibrous tissue, and some specimens showed irregular deposits of exudates and pink-staining hyaline material in the outer nuclear and molecular layers. Rods and cones were destroyed, and pigmented debris was present between the external limiting membrane and Bruch's membrane. There were hemorrhages in the inner layers of the retina. The choroid was thin and atrophic; its vascularity was decreased, and the choriocapillaris was obliterated. Irradiation cataract was characterized by "bladder cells" at the equator and the posterior cortex. In one case the lens epithelium completely surrounded the lens.

We have had the opportunity to study pathologically an eye with retinoblastoma which had been treated by radon seed implantation along with a small amount of external radiation. The sites of radon seed attachment to the globe were very obvious on the pathological specimen and, therefore, the approximate radiation dosage to various parts of the globe could be calculated and related to the histological changes observed. For this reason it was deemed worth while to make this report.

Report of a Case

The patient was first seen at Stanford University Hospital * in December, 1954, at the age of 5 months, with a referring diagnosis of bilateral retinoblastoma. Examination under general anesthesia revealed bilateral, symmetrical retinoblastoma filling the macular area of both eyes and barely extending across the path of the superior and inferior temporal vessels. Each was approximately 8 disc diameters in size, crudely round in outline, and about 9 D. elevated. Because of the close similarity of the tumors it was decided to treat both by irradiation and TEM.

From Dec. 23, 1954, to Jan. 14, 1955, each eye received a total of 3000 r in air (1650 r calculated tumor dose) via external temporal portals. Administration of TEM by mouth was begun on Dec. 22, 1954, and was continued on an almost weekly dosage until November, 1955. By Jan. 20, 1955, both tumors showed definite shrinkage. On Feb. 10, 1955, in each eye two radon seeds were sewn to the sclera, straddling the tumor with long axis parallel to the limbus. In the left eye, the eye being reported on here, the posterior seed was 0.56 mc. in strength; the other, 0.52 mc. Further shrinkage and degeneration of the tumors occurred until they were yellowish white and almost flat.

In August, 1955, several suspicious areas appeared in the nasal retina of the left eye. By the end of October it was fairly certain that this represented a recurrence of the retinoblastoma. On Nov. 17, 1955, the left eye was enucleated.

In the fall of 1956 a tumor recurrence was noted in the right eye below the disc. The child was then treated with an additional 6000 r delivered by the linear accelerator, a new machine designed to direct the radiation to the tumor area with minimal effect to other tissues.

Grossly the left eye specimen was a hard eyeball with 10 mm. of optic nerve attached, measuring 19×20×20 mm. The anterior segment was not remarkable. Posteriorly the two radon seeds were still sutured in place to the sclera, the posterior one being approximately 2 mm. from the optic nerve. The seeds were removed prior to horizontal sectioning of the globe. The vitreous was liquid and clear. In the macular area a

* The patient was originally referred by Dr. John Gallaher of Walnut Creek, Calif., to Dr. A. Edward Maumenee. Both physicians made their records available. One of us (E. T.) has been able to follow the patient closely from December, 1954, to the present.

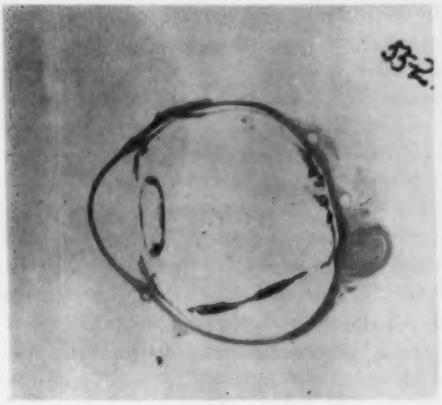

Figure 1

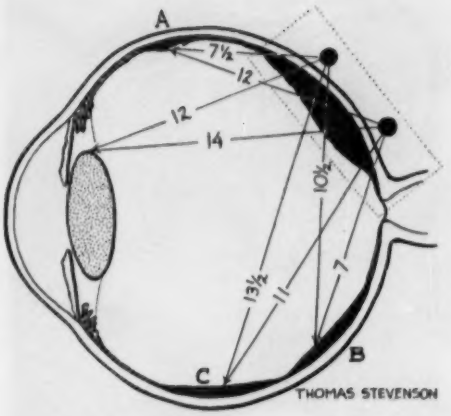

Figure 2

roughly circular slightly elevated mass measuring approximately 10×9 mm. was seen. On the nasal side of the interior of the globe several small white tumor nodules were noted. The lens appeared normal.

A horizontal section (Fig. 1) shows two round defects on the surface of the posterior sclera representing the sites of the radon seeds. Suture tracks are visible next to the defects, and both suture and radon tracks are well encapsulated.

Figure 2 is a drawing giving the measured distances between radon seeds and tumor nodules and lens. Figure 3 gives the measured distances between the radon seeds and adjoining choroid, retina, and optic nerve. The distances are recorded in millimeters.

One of us (P. T.) has calculated the radiation dosage from radon seeds alone to various parts of the globe. This is summarized in the Table. As indicated in the notes below the Table, these are approximate dosages. However, we can still observe the relative effect on various intraocular tissues.

A number of interesting observations can be made from the histological sections. The optic nerve, receiving over 5000 r at its temporal margin from the radon seeds, appears normal (Fig. 4). Figure 5 shows the calcified remains of the original tumor mass

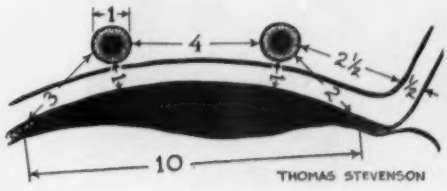

Figure 3

Radiation Dosage from Radon Seeds Alone to Various Parts of the Globe

Posterior seed: 0.56 mc. × 133 hr.=74.5 mc.-hr.
Anterior seed: 0.52 mc. × 133 hr.=69.0 mc.-hr.

Dosage from radon seeds only at	Dose, r
1. Tumor A	1,370
2. Tumor B	1 700
3. Tumor C	810
4. Lens	700
5. Optic nerve margin	5,980
6. Distal end of fibrosed choroid	5,800
7. Proximal end of fibrosed choroid	9,870
8. Calcified tumor residual opposite posterior seed (1 mm. from seed)	22,500
9. Calcified tumor residual opposite anterior seed (1 mm. from seed)	21,400
10. Original tumor apex assumed at a point 4 mm. from each seed and 3 mm. from sclera	6,100
11. Distal residual tumor edge	5,570
12. Proximal residual tumor edge	5,930

1. Add to these doses a tumor dose of 1650 r received by external irradiation. Factors: KV_p 200; filtration, 0.5 mm. Cu and 0.5 mm. Al; Ma 20; TSD 34.5; H.V.L. 1.25 mm. of Cu. Air Dose: 3000 r in 10 treatments through opposing lateral circular ports 2.5 cm. in diameter with anterior chamber shielded.

2. No part of the original tumor mass received less than 5570 r by radon alone.

3. The parts of the tumor directly under the radon seeds received extremely high doses, which are calculated here as about 22,000 r. It must be understood, however, that dose calculations at such small distances from the source are nearly meaningless, as a change in distance of only 0.5 mm. would make a difference of about 14,000 r, or nearly 64%. Also, isodose curves for such distance are not available and for closer approximation of dose one would have to integrate dose along the length of the seed. Even at distances of 4 mm. an error of measurement of 0.5 mm. would introduce an error in dosage of close to 25%. At any rate, it should be kept in mind that there is a high increasing dosage gradient toward the radon sources.

4. The calculated dose received by the apex of the original tumor assumes a tumor thickness of 3 mm. at the start of therapy.

5. These dosage calculations do not include any contributions by β-radiation, which is negligible—certainly for anything beyond 1 to 2 mm. from the source.

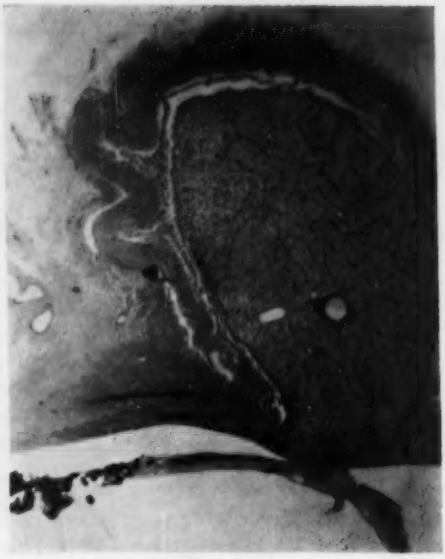

Figure 4

in the macula. The retina and tumor in this region, receiving from about 5000 r to 20,000 r from the seeds, depending on the proximity to the seeds, are completely destroyed. The sclera in this region is only slightly altered, in spite of heavy dosage from the seeds. There was slight loss in its cellularity and it did not stain so deeply as did the anterior sclera on that side. Its blood vessels appeared unaffected. In contrast, the choroidal vessels in this same area were almost completely obliterated. The portion of choroid most distant from the seeds and still fibrosed received approximately 5800 r from the radon source.

Figure 6 shows a viable tumor focus on the temporal side of the globe near the ora serrata. This area received approximately 1370 r from the radon seeds. Here the retinoblastoma is seen to arise from the outer layers of the retina. From time to

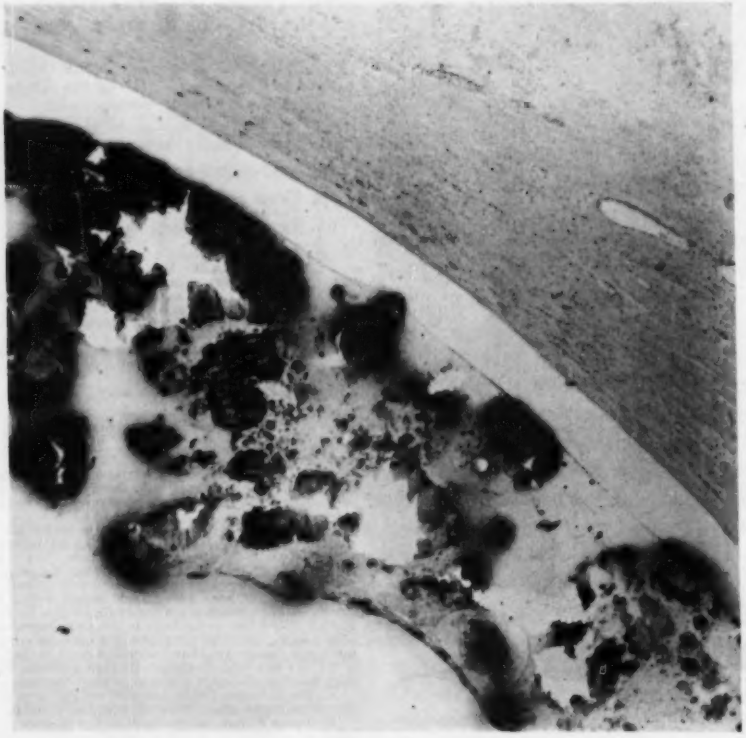

Figure 5

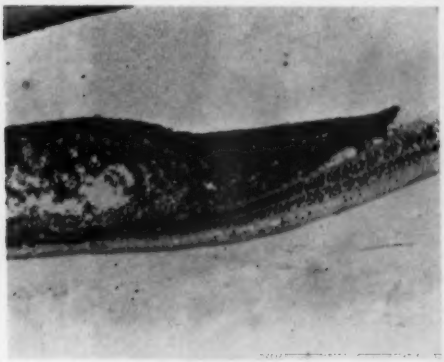

Figure 6

Figure 7

time the question of which retinal layer may give rise to retinoblastoma comes up for discussion. Some have claimed that retinoblastoma arises only from the inner retinal layers. From this Figure and from other slides it appears that this tumor may arise from any retinal layer.

Figure 7 shows two viable tumor foci on the nasal side. Tumor B received approximately 1700 r, and Tumor C, about 800 r from the radon seeds. The presence of these multiple foci points up the difficulty in treating a multicentric neoplasm such as retinoblastoma with radon seeds.

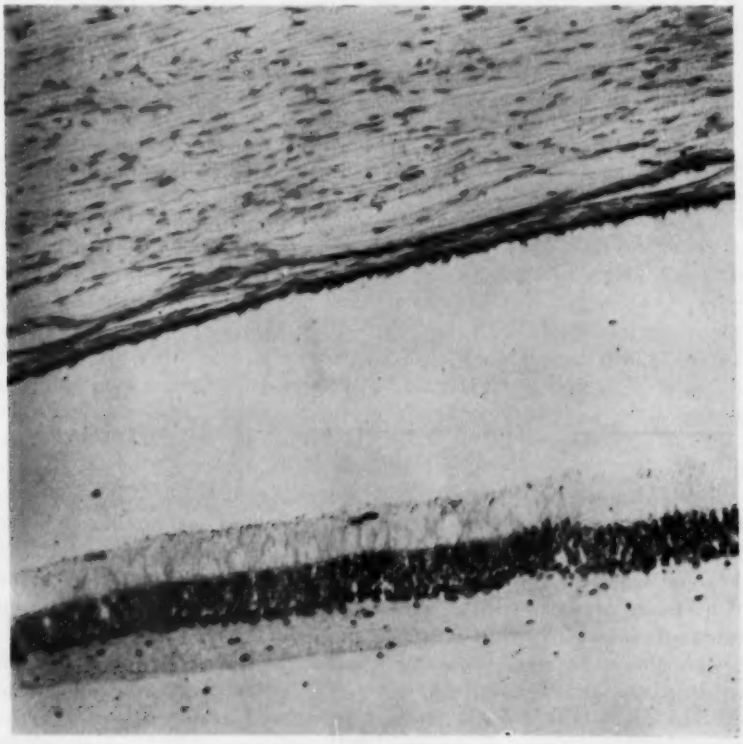

Figure 8

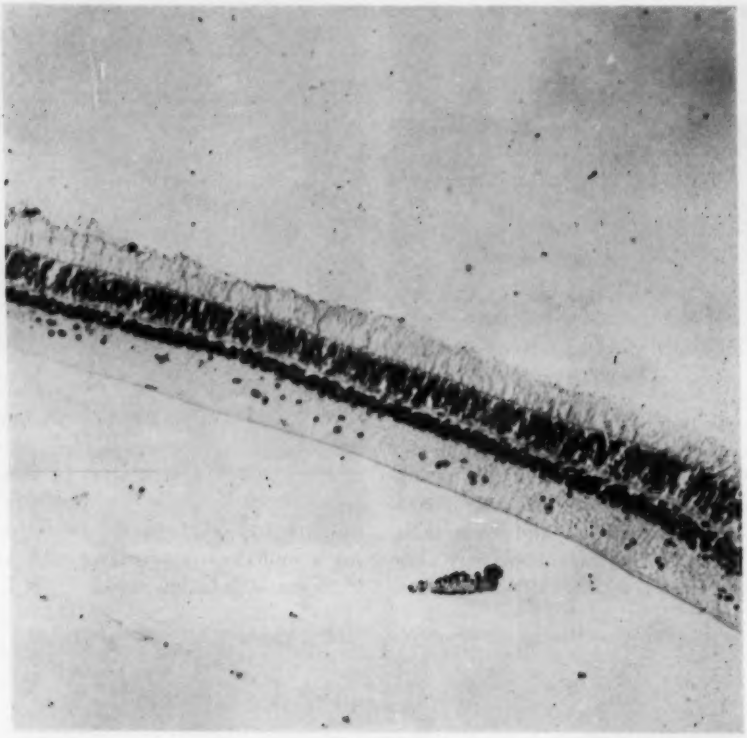

Figure 9

On the temporal side beyond the limits of the calcified tumor residual the retina reveals a marked decrease in the ganglion cells (see Figures 6 and 8), possibly due to greater susceptibility of these cells to radiation or to an effect on the retinal vascular supply in this area. From the calculated dosage, as little as 1400 r can cause severe damage to the ganglion-cell layer.

Just anterior to the necrotic tumor on the temporal side there is a fusion of the inner and outer nuclear layers and obliteration of the outer plexiform layer (Fig. 8). As one goes further anteriorly the nuclear layers become distinct and separate and the outer plexiform layer appears (Fig. 9). The number of nuclei in the inner nuclear layer in the region of fusion is reduced when compared with the same layer more anteriorly or, especially, on the nasal side of the eyeball. The death of cells of the inner nuclear layer from irradiation and the subsequent degeneration of their axones could explain the disappearance of the outer plexiform layer. The approximate dosage of radiation to this region was 5000 r. Cibis and Brown [11] reported pyknosis of the rod and bipolar nuclei in monkeys subjected to irradiation. We do not see this in our specimen. However, they were reporting the acute effects of irradiation within 96 hours after exposure, whereas we are reporting the relatively long-term effects of irradiation. In the inner nuclear layer of this specimen some cells may have undergone pyknosis and karyorrhexis before their death. It has been suggested [12] that the changes in the nuclear layers of the retina in this specimen could be the result of occlusion of a large retinal artery by the tumor rather than the result of irradiation.

The retinal vessels on the irradiated side are reduced to fibrous cords (arrows, Fig. 10) and appear to be more affected than

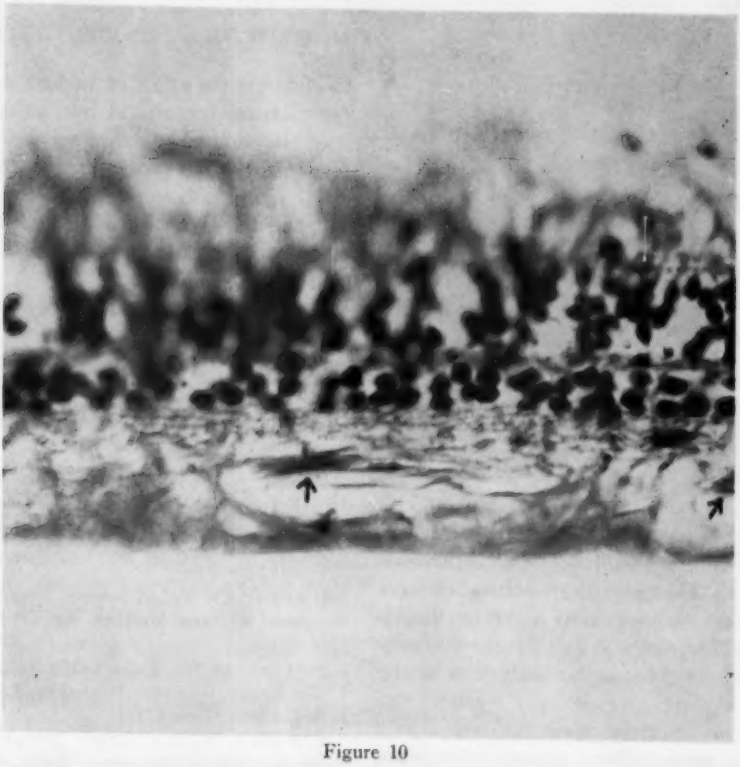

Figure 10

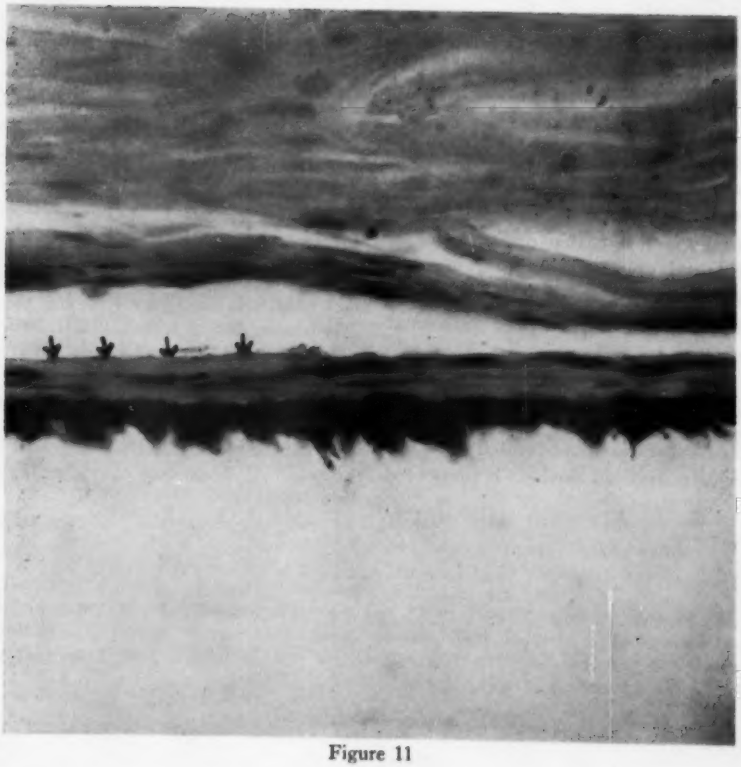

Figure 11

Figure 12

choroidal vessels of larger caliber but equal distance from the radiation source (arrows, Fig. 11). The mild degenerative changes seen in the rod and cone layer on the irradiated side (Figs. 8 and 9) are probably secondary to the vascular occlusions in the choroid.

The lens received approximately 700 r from the seeds. There appear to be some early abnormal changes in the lens "bow" at the temporal equator (Fig. 12). There is some disorganization to the pattern of the nuclei in the cortex, with some nuclei migrating to the posterior cortex.

It is again pointed out that to these radon seed dosages must be added a small amount for the external radiation applied (1650 r tumor dose). The possible contribution of the TEM to these observations cannot be evaluated, but it was probably insignificant, inasmuch as tumor recurred while the patient was taking this drug.

Summary

A case of retinoblastoma treated with external radiation and radon seeds is presented to illustrate the effect of various dosages of radiation on tumor and normal ocular tissues. In addition to the effect on the retinoblastoma, changes due to radiation were noted in the adjoining sclera and choroid, ganglion-cell layer, inner nuclear layer, and outer plexiform layer of the retina, retinal blood vessels, and lens.

Stanford University Hospital, Clay and Webster Sts. (15).

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Ocular Manifestations of Sickle-Cell Disease

GEORGE GOODMAN, M.D.; LUDWIG von SALLMANN, M.D., and MONTE G. HOLLAND, M.D.,
Bethesda, Md.

The tendency for red blood cells to assume a sickled shape under conditions of low oxygenation has been demonstrated predominantly in the Negro race.[1] Patients exhibiting this phenomenon have been classified as having sickle-cell trait, an asymptomatic carrier state, or sickle-cell anemia, a hemolytic disease with occlusive vascular complications and shortened life span. Renewed clinical interest in these entities has followed recent developments in the study of human hemoglobins.

In 1949, Pauling, Itano, Singer, and Wells[2] proved by means of electrophoresis that the hemoglobin in patients with sickle-cell anemia (sickle-cell hemoglobin, or hemoglobin S) differs from normal adult hemoglobin (hemoglobin A). Furthermore, familial electrophoretic studies[2] and the genetic investigations of Neel[3] established the hereditary basis for the sickling phenomenon. The inheritance of the gene for sickle-cell hemoglobin from one parent and the gene for hemoglobin A from another parent, constitutes the sickle-cell trait and represents a heterozygous state. The inheritance of the gene for sickle-cell hemoglobin from both parents results in sickle-cell anemia, the homozygous state. Subsequent studies[4,5] disclosed that the sickling process is directly dependent upon the unique properties of sickle-cell hemoglobin, which becomes insoluble and gels when deoxygenated. This results in the formation of sickled erythrocytes, which are prone to hemolysis, and the development of viscous aggregates of sickled cells, which may cause vascular obstructions.

Electrophoretic hemoglobin studies have led to the identification of several other genetically controlled abnormal hemoglobins. When they coexist with sickle-cell hemoglobin clinical syndromes result which are similar to sickle-cell anemia but are usually less severe.* Such heterozygous hemoglobin states include sickle-cell hemoglobin C disease and sickle-cell hemoglobin D disease. The association of sickle-cell hemoglobin with other hereditary erythrocyte abnormalities has also been reported, namely, sickle-cell thalassemia disease and sickle-cell congenital hemolytic icterus. These new entities are usually grouped with sickle-cell anemia under the general heading of sickle-cell disease.

Sickle-cell hemoglobin C disease is the commonest of the newly discovered variants of sickle-cell disease; it is estimated to be present in 10,000 to 20,000 American Negroes.[6,9] It may be suspected hematologically when the sickling phenomenon is associated with a high percentage of target cells. The clinical course is usually milder than that of sickle-cell anemia, but it may vary from an asymptomatic condition to a picture simulating the anemia. Many cases of sickle-cell disease, diagnosed as the trait or anemia before the advent of hemoglobin electrophoresis, have now been found to represent sickle-cell hemoglobin C disease.[10,11]

This study deals with the ocular changes in five patients with sickle-cell disease. Hemoglobin electrophoresis established a

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare.

* For comprehensive reviews of the abnormal hemoglobins and their clinical manifestations, see Chernoff[8]; Itano, Bergren, and Sturgeon,[7] and Zuelzer, Neel, and Robinson.[8]

diagnosis of sickle-cell hemoglobin C disease in four patients and suggested sickle-cell hemoglobin D disease in the fifth case. The significance of the eye findings is discussed.

Report of Cases †

CASE 1.—A 38-year-old Negro housewife noted "seaweed" before her left eye on Feb. 19, 1956, without other ocular discomfort. The ophthalmologist who was consulted four days later described periphlebitis and fibrous tissue proliferation in the periphery of both fundi and three areas in the left eye which had the characteristics of retinal tears. On the basis of the ophthalmoscopic findings and a history of tuberculosis in two aunts and a former roommate a diagnosis of tuberculous eye disease was made, and a course of dihydrostreptomycin, aminosalicylic acid, and isoniazid was begun. The patient was referred to the Ophthalmology Branch of the National Institutes of Health on Feb. 29, 1956, for further diagnostic studies.

Four years previously the patient had had a similar visual disturbance in her left eye which disappeared within a few days. There had been no new ocular symptoms until the present episode.

The patient suffered from arthralgias as a child. Ten years previously she had had a painful left knee for several days which was labelled as "rheumatism." There was no history of jaundice or anemia. A sister died of sickle-cell disease at the age of 34; jaundice, anemia, and joint pains were the major manifestations.

The patient was followed in the clinic for one week, with no change in ocular signs or symptoms. She was hospitalized on March 7, 1956, for completion of diagnostic studies.

Physical Examination.—Visual acuity was 20/15 O. D. and 20/20 O. S. without correction. External and slit-lamp examination of the anterior segments of both eyes did not reveal abnormalities except for fine opacities in the lens cortex bilaterally. A cellular vitreous haze was present in the left eye, consisting predominantly of red blood cells. The right vitreous was clear.

Ophthalmoscopy disclosed a generalized tortuosity of the retinal arterial tree in both eyes, with normal optic disks and macular areas.

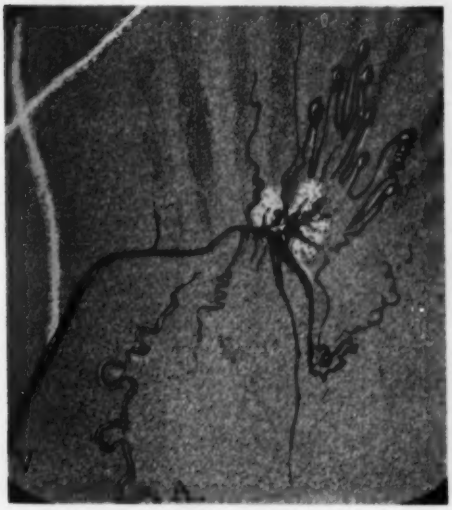
Left Eye: Clumps of cottony white material in the vitreous obscured the inferior part of the fundus. Four patches of glial or fibrous proliferation occupied the temporal retina and protruded into the vitreous, with "pipestem" sheathed vessels evident peripherally (Fig. 1). Tortuous anastomoses of retinal vessels marked the border of these white masses, with fine branches running along the surface. Adjacent to the patch at two o'clock a small circumscribed flat area of detached retina was present, traversed by a beaded venule. A sharply outlined red patch, lying in or on the retina and resembling a retinal tear, was noted in the lower temporal periphery.‡ In the superior fundus vascular pathology centered about the dilated segment of a venule, from which vascular loops grew into the vitreous, terminating in bulbous dilatations (Fig. 2). A nasal branch of the venule showed "pipestem" sheathing. The nasal periphery at about three o'clock contained two localized areas of distorted vascular architecture involving both arterioles and venules (Fig. 3).

† The following physicians referred cases to the Ophthalmology Branch for study: Dr. Pearl Watson, Washington, D. C. (Case 1); Dr. Frederick Stohlman, National Cancer Institute, Bethesda, Md. (Cases 2 and 3); Drs. Ben Fine, Jack Gilligan, and Paul McCurdy, District of Columbia General Hospital, Washington, D. C. (Case 4). Case 5 was called to our attention by Drs. Lorenz Zimmerman and C. F. Vorder Bruegge, of the Armed Forces Institute of Pathology. Dr. F. L. Jennings, of the Veterans' Administration Hospital, Indianapolis, and Dr. Lorenz Zimmerman cooperated in making available clinical data and a blood specimen for electrophoretic study. This patient has been briefly reported elsewhere (Case 3 of Henry and Chapman[20]).

‡ The use of the term "peripheral" or "periphery" in this paper to describe the location of retinal lesions refers to the limits of fundus visualization with direct ophthalmoscopy through a maximally dilated pupil.

Fig. 1 (Case 1).—Temporal periphery, O. S. Multiple fibrous and/or glial patches associated with tortuous anastomosing vessels and vascular sheathing. A small circumscribed serous retinal detachment is present proximal to the patch at 2 o'clock.

Fig. 2 (Case 1).—Superior periphery, O. S. A swollen venous segment from which vascular loops project toward the vitreous, terminating in bulbous dilatations. Other changes include sheathing of a venule, arteriolar tortuosity, and the presence of fine vascular twigs probably representing early neovascularization.



Beading and aneurysmal dilatations predominated in the venules; tortuosity was the major change in the arterioles.

Right Eye: A dense elevated mass of fibrous or glial tissue, from 4 to 7 disk diameters in size, covered the fundus in the lower temporal periphery. An arteriole and venule entered the mass but could not be distinguished beyond its nasal border. In the nasal periphery at about three o'clock an arteriole and a venule became part of an anastomosing network of vessels (Fig. 4). Berry-shaped aneurysms were present along the border of the vascular network.

The general physical examination was notable for the absence of splenomegaly and the presence of a healed scar above the medial malleolus of the left leg of the type frequently seen in sickle-cell anemia.

Diagnostic Studies.—Serologic tests for syphilis, tularemia, and brucellosis were negative. The Toxoplasma dye test was positive in a 1:256 dilution. Skin testing resulted in positive reactions to toxoplasmin

Fig. 3 (Case 1).—Nasal periphery, O. S. An irregular network of arterioles and venules with patchy glial or fibrous proliferations. Tortuosity predominates in the arterioles, and beading and aneurysmal dilatations, in the venules.

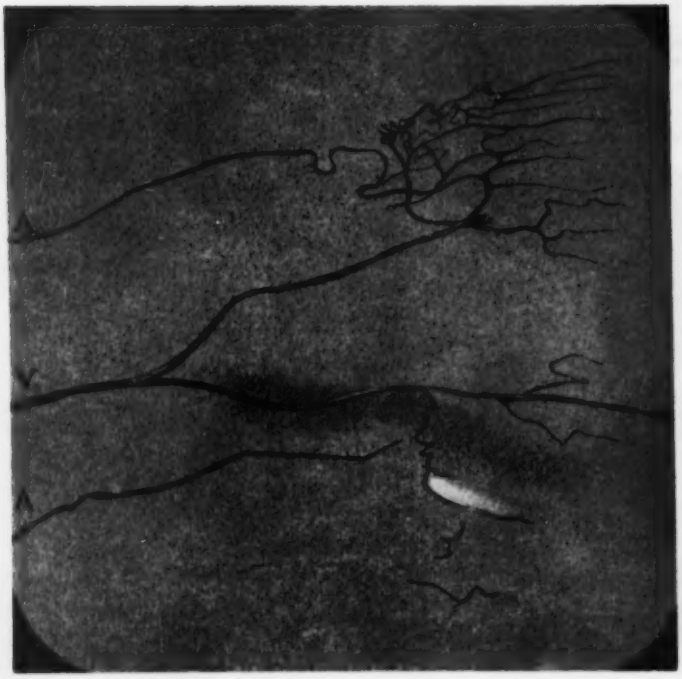


Fig. 4 (Case 1).—Nasal periphery, O. D. Superiorly there is an arborizing vascular network derived from an arteriole and venule. Inferiorly a venule shows irregular branching.

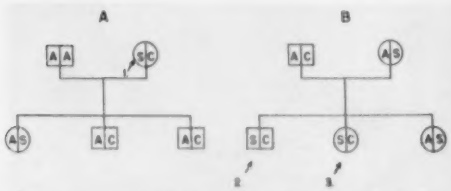


Chart showing inheritance of sickle-cell hemoglobin (*S*), hemoglobin C (*C*), and normal adult hemoglobin (*A*) in the families of Cases 1, 2, and 3. For percentage of hemoglobin, see text.

and PPD (second strength). There were no reactions to first and intermediate strength PPD or to Staphylococcus, Streptococcus, coccidioidin, and lymphogranuloma venereum antigens.

Hematologic studies showed a consistent leukocytosis (10,000 to 13,000), mild anemia (10 to 13 gm. of hemoglobin), positive sickle-cell preparations, and numerous target cells. Red blood cell indices were as follows: mean corpuscular hemoglobin, 20$\mu\gamma$; mean corpuscular hemoglobin concentration, 28%, and mean corpuscular volume, 77 cu. μ. Reticulocyte counts varied from 2% to 3%. Platelet count, bleeding time, clotting time, and prothrombin time were normal. There was a decrease in osmotic fragility of the red blood cells.

The Chart summarizes the distribution of hemoglobin types in this family as determined by hemoglobin electrophoresis (Tiselius method). The findings are given in Table 1.

Repeated urinalyses disclosed a consistent 2+ albuminuria, numerous red blood cells and/or white blood cells, and granular casts. Many oval fat bodies and fatty casts were present. Renal clearances and concentrating ability were depressed. Urine cultures revealed an unidentified Gram-negative rod in one instance and was negative on two other occasions.

Blood urea nitrogen was 13 to 19 mg. per 100 cc., and serum creatinine was 0.8 to 1 mg. per 100 cc. Direct- and indirect-reacting serum bilirubin was normal. Serum cholesterol was 280 mg. per 100 cc.; the total protein was 6.8 gm. per 100 cc., and the A/G ratio was 3:3.8.

X-ray of the skull showed a circumscribed area of decreased density interpreted as a developmental defect. Mucosal thickening was present in the ethmoid sinuses. X-rays of the chest, cervical spine, thoracic spine, lumbar spine, hands, knees, ankles, feet, hips, and pelvis were normal. An intravenous urogram demonstrated irregular and blunted kidney calyces and dilation of the pelvis bilaterally.

Course.—Within 10 days after hospitalization the bright red patch in the lower temporal periphery had disappeared. The vitreous hemorrhage cleared gradually, but the serous retinal detachment remained unchanged during the month of hospitalization. There were no systemic complaints. The patient was discharged on March 30, 1956. In view of the history of exposure to a roommate with active pulmonary tuberculosis and the positive tuberculin test, the possibility of a tuberculous etiology could not be excluded. Accordingly, she was placed again on an antituberculous regimen (streptomycin 0.5 gm. three times a week and isoniazid 300 mg. daily) as an outpatient.

On April 28, 1956, the patient noted a bright red flash in her left eye, followed by

TABLE 1.—*Distribution of Hemoglobins in Members of the Families of Patients 1, 2, and 3*

	Hemoglobin A, %	Hemoglobin S, %	Hemoglobin C, %	Diagnosis
Family A				
Mother (Case 1)	--	52	48	Sickle-cell hemoglobin C disease
Father	100	--	--	Normal
Son	67	--	33	Hemoglobin C trait
Son	67	--	33	Hemoglobin C trait
Daughter	60	40	--	Sickle-cell trait
Family B				
Mother	65	35	--	Sickle-cell trait
Father	75	--	25	Hemoglobin C trait
Son (Case 2)	--	47	53	Sickle-cell hemoglobin C disease
Daughter (Case 3)	--	45	55	Sickle-cell hemoglobin C disease
Daughter	64	36	--	Sickle-cell trait

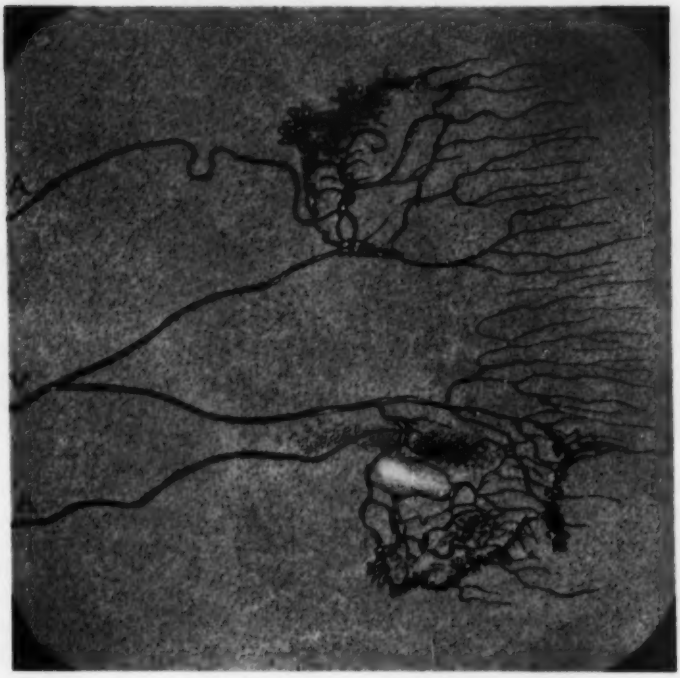


Fig. 5 (Case 1).—Nasal periphery O. D. This is the lesion depicted in Figure 4, one month later. The upper vascular network is denser, with an increase in number and size of saccular aneurysms. Similar changes have developed below from branches of an arteriole and venule.

a haze which greatly reduced vision. She was readmitted to the National Institutes of Health on May 2, 1956. The visual acuity of the left eye was reduced to 20/50. Many red cells and several red masses were dispersed in the vitreous. A few small bright red patches, strikingly similar to retinal tears, were noted in the far inferior temporal periphery, apparently in the retina. Otherwise, fundus details as observed through the vitreous haze, and confirmed when vitreous clearing had occurred, resembled those seen on the previous admission.

The lesions in the right eye appeared unchanged except for some increase in vascular pathology in the nasal periphery (Fig. 5). As compared with the first examination (Fig. 4), the upper arborization showed an increase in caliber and number of anastomosing vessels and berry-shaped aneurysms. More dramatic changes were present below this area, where the small tortuous branches of the lower venular branch, the adjacent isolated vascular tufts, and the neighboring arteriole, all noted on the previous examination (Fig. 4), were now incorporated in a dense anastomosing network.

The red patches in the left eye changed position repeatedly and disappeared within the first few days. The large red masses in the vitreous became slowly transformed into white cottony masses. At the time of the patient's discharge the vitreous was free of red blood cells or red masses but white cottony substance persisted inferiorly. Visual acuity was 20/20 without correction in both eyes.

In contrast to the patient's feeling of well-being during the first hospitalization, she now complained of weakness and occasional sharp left upper quadrant abdominal pain, which were accompanied by a low-grade fever, elevated white blood cell count, and a decrease in hemoglobin of about 2 gm. in comparison with that of the previous hospital admission. On May 25, 1956, a transfusion of 500 cc. of whole blood was begun. After receiving 450 cc. of blood,

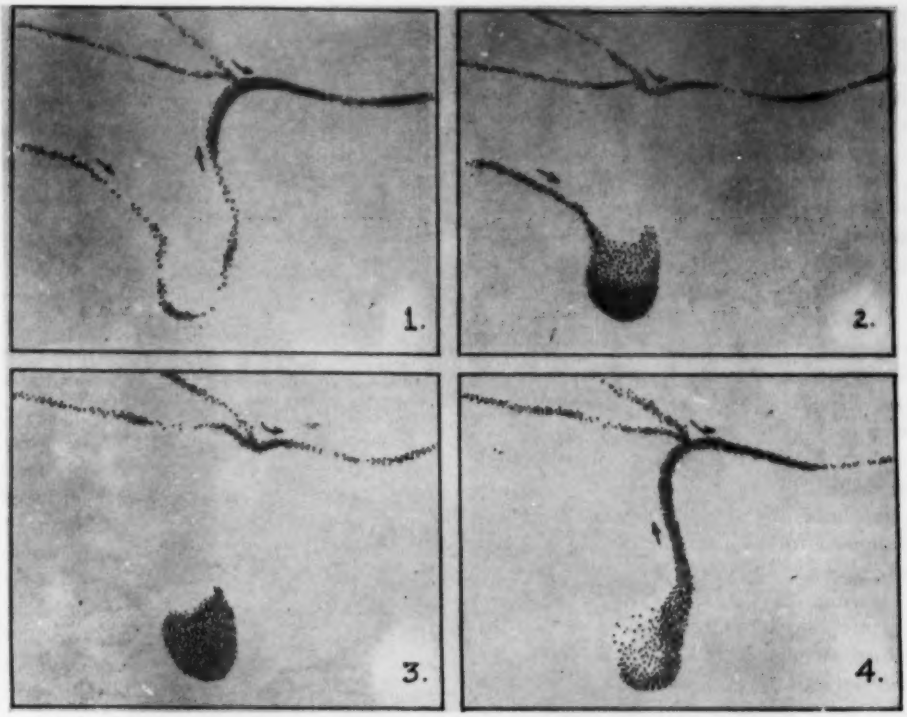


Fig. 6 (Case 1).—Bulbar conjunctival vessels, O. S. A sketch of changes in the appearance of blood flow in a paralimbal vessel containing a microaneurysm observed over a period of about one minute. The stage at which cells have pooled in the aneurysm, and the afferent and efferent channels are empty of blood, simulates a petechia. Drawings were made under × 40 magnification of a slit lamp.

the patient experienced a brief chill followed by joint pain which lasted for the next three days. The recheck of blood typing confirmed earlier results; blood culture and a direct Coombs' test were negative; serum bilirubin remained normal, and there was no hemoglobinuria.

Following the transfusion there was subjective improvement, and the patient was discharged on June 5, 1956. In follow-up examinations during the next four months no significant change in the retinal pathology was observed. However, at the patient's last visit a careful examination was made of the conjunctival vessels with use of the slit-lamp biomicroscope at a fortyfold magnification. The findings included circumscribed dilations of small vessels in many areas, with dense packing of the red blood cells and diminished flow in these dilated segments. Particularly interesting was the presence of microaneurysmal dilations in the paralimbal conjunctival vessels (Fig. 6).

Comment.—The patient is a 38-year-old Negro housewife who was hospitalized twice in two months because of recurrent vitreous hemorrhage in the left eye, with a history suggesting a similar episode four years previously. Hematologic investigation established a diagnosis of sickle-cell hemoglobin C disease. The fundus pathology, vascular in nature, embodied all the major findings in the reported cases of sickle-cell disease with retinopathy (see General Comment). It is noteworthy that an ocular complication was the first clinical manifestation to result in hospitalization and the recognition of a hemoglobin disorder.

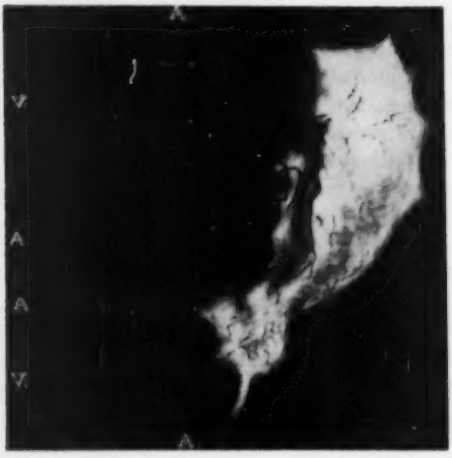
Extraocular clinical symptomatology secondary to the presence of sickle-cell hemo-

globin was restricted to joint and muscle pain in childhood. An exacerbation of symptoms followed a blood transfusion during the patient's second hospitalization; similar complications have been reported in other cases of sickle-cell disease following compatible blood transfusions.[12] The kidney pathology, evidenced by the findings on urinalysis and intravenous urography, was of uncertain etiology. However, recent reports of a variety of renal abnormalities in sickle-cell disease, ranging from functional changes [13,14] to gross hematuria [15] and the nephrotic syndrome,[16] suggest that the kidney disease in this case may also have been secondary to the hemoglobin disorder.

CASE 2.—A 15-year-old Negro youth has sickle-cell hemoglobin C disease and no complaints referable to the eyes. He was examined for evidence of ocular pathology on April 25, 1956.

During childhood the patient was frequently hospitalized for arthralgias, which ceased at the age of 12. Since then he has had only occasional transitory episodes of joint pain, lasting a few hours, and occurring twice a year.

Fig. 7 (Case 2).—Temporal periphery, O. S. A large fibrous and/or glial patch with tortuous and anastomosing venules and arterioles at its proximal border and within its substance. Adjacent to its lower temporal border is a sharply circumscribed bright red patch simulating a retinal tear. It probably represents a thin layer of preretinal hemorrhage.



Physical Examination.—The visual acuity of both eyes was 20/15, and no abnormalities were present on external examination and biomicroscopy of the anterior segments.

A large elevated mass of fibrous or glial tissue covered a part of the lower temporal periphery of the left eye, with tortuous vessels in its substance and at its borders (Fig. 7). Immediately adjacent to the lower temporal border of the mass a sharply outlined homogeneous red patch was lying next to or in the retina, simulating a retinal tear. In the superonasal periphery tortuous arterioles and venules formed a loose anastomosing system (Fig. 8).

Areas of vascular pathology were scattered through the superior and nasal periphery of the left eye. These included complete sheathing and/or obliteration of arterioles and venules and irregularities in caliber and abrupt terminations of their blood columns. Adjacent to sheathed or obstructed vessels twisting new vascular twigs were apparent, sometimes without visible connection to nearby vessels (as in Case 1, Figs. 2 and 4); at other places they gave rise to a convoluted network anastomosing with neighboring vessels (analogous to Fig. 7). Patchy areas of chorioretinal atrophy in the inferior and temporal periphery were similar to those seen in the third patient (Fig. 9). Fundus examination of the right eye revealed a round discrete silvery gray lesion in the superior periphery, appearing like a healed focal choroiditis; it was surrounded by glittering specks.

Course.—May 28, 1956: The red patch in the lower temporal periphery O. S. still resembled a retinal tear, but it was faded and smaller. Serial sketching showed positional changes in relation to an underlying artery. This suggested that the red patch was anterior to the retina and probably represented a thin layer of preretinal hemorrhage.

Aug. 2, 1956: The large red patch had disappeared, but residues of it were scattered along the temporal margin of the glial

Fig. 8 (Case 2).—Superior retina, O. S. A loose anastomosing network derived from arterioles and venules.

mass. Several punctate red spots were noted on the surface of the left disk.

The bulbar conjunctival vessels of both eyes on biomicroscopy exhibited saccular and sausage-like dilatations of fine branches which contained densely packed red blood cells. These changes appeared and disappeared frequently within the hour, as a sign of their functional nature, but continued to be seen in subsequent examinations.

Aug. 24, 1956: As compared with the previous examination, fine branches of a venule had extended about 1 disk diameter closer to the glial mass in the left eye, and at the point of a terminal loop two small berry aneurysms and a varicose aneurysm were noted. The small red spots on the temporal half of the optic disk were more prominent and were joined by others in the adjacent retina. The topical relation of two of these dots to small vessels suggested pinpoint saccular aneurysms.

March 13, 1957: The punctate red spots on the optic disk of the left eye were replaced by a fine capillary network. A bright red patch was again seen temporal to the glial patch in the left eye.

Examination of the right eye revealed a variety of lesions which had not been seen on the previous examination. Arterioles and venules terminated abruptly in the preequa-

torial region nasally, and a short distance distal to the obstruction tortuous vascular twigs had developed, occasionally terminating in a small red knob suggesting a terminal aneurysm. Two arterioles in this area became attenuated and could not be distinguished for short distances and then appeared to continue as sharp chalk-white lines. This was almost identical with the appearance of the retinal vessels in Case 5 (Fig. 20). A larger venule, about 4 disk diameters from the optic disk, showed focal narrowing, with a markedly dilated and cyanotic distal segment. Sheathing of both arterioles and venules was also visible.

Diagnostic Studies.—Toxoplasmin skin test, test with second strength PPD, and Toxoplasma dye test were negative.

Hematologic studies showed a hemoglobin of 12 gm., a hematocrit value of 32%, positive sickling preparations, and numerous target cells. Platelet count, bleeding time, coagulation time, and prothrombin time were within normal limits. The red blood cell indices were as follows: mean corpuscular hemoglobin 28$\mu\gamma$; mean corpuscular hemoglobin concentration 37%; mean corpuscular volume, 78 cu. μ.

The Chart illustrates the distribution of hemoglobin types in the patient and his family as determined by hemoglobin electrophoresis (Tiselius method). The findings are given in Table 1.

Routine urinalysis was completely negative, and a test of urinary diluting ability was normal. Determination of the maximal urinary osmotic pressure by the freezing point method, after 12 hours of water deprivation and vasopressin (Pitressin) injection, showed a decrease in urinary concentrating ability. This testing procedure, described by Keitel, Thompson and Itano,[18] was also used in Case 3.

A healed Ghon complex was observed on chest x-ray.

Coment.—Case 2 is that of a 15-year-old Negro boy with sickle-cell hemoglobin C disease and no ocular complaints. A routine eye examination disclosed the presence of vascular retinopathy and preretinal hemorrhage in the left eye similar to the findings in Case 1. During the course of observation vascular changes also became manifest in the right eye. The patient had a history of joint and muscle pain during the first 10 years of life, which necessitated hospitalization on several occasions.

Case 3.—A 14-year-old Negro girl has sickle-cell hemoglobin C disease and no eye complaints. She was examined for evidence of ocular pathology on April 17, 1956. She is the sister of Patient 2.

The patient has had intermittent joint and muscle pains since the age of one year. During the previous few years these have been associated with abdominal pain and jaundice, occurring about every four to six weeks. Severe crises necessitated frequent hospitalizations and blood transfusions. Because of the occurrence of several episodes of severe left upper quadrant pain and tenderness during the previous year, recurrent splenic infarctions were suspected, and a splenectomy was performed on April 25, 1956. Pathologic examination of the spleen demonstrated hemosiderosis, multiple subcapsular infarcts, thrombosed and partially calcified end-arteries, and fibrous thickening of the sinusoidal walls. In the year following splenectomy the patient has not had abdominal pain, nor has she required blood transfusions.

Physical Examination.—Corrected visual acuity was 20/20 in both eyes. External examination and biomicroscopy of the cornea, anterior chamber, and lens were normal in both eyes.

A localized area of pigmentary disturbance with a scalloped gray-white border was located in the midtemporal periphery of the right fundus, with small irregular venular branches at the borders of the lesion (Fig. 9*A*). A similar lesion was seen in the inferior periphery of the left eye (Fig. 9*B*). In the temporal periphery of the left eye a round discrete area of heavy pigmentation was present, resembling a patch of healed focal choroiditis. There appeared to be an

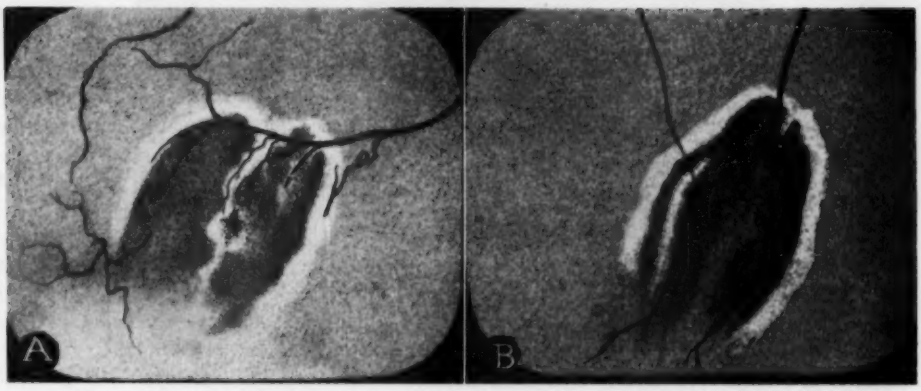


Fig. 9 (Case 3).—Nasal periphery O. D. *A* and inferior periphery O. S. *B*. Localized areas of hyperpigmentation with circumscribed white borders. An increase in branching and tortuosity of a venule is noted in *A*.

increase in the number and tortuosity of small vessels in the retinal periphery of both eyes.

Follow-up examinations of the fundus were made during the next six months and no further changes were noted. The conjunctival vessels, however, showed findings similar to those described in the conjunctiva of the patient's brother (Case 2): sausage-like dilatations in the course of fine vessels, with densely packed red blood cells within these dilated segments.

Diagnostic Studies.—The Toxoplasma dye test was positive undiluted. A toxoplasmin skin test and test with second-strength PPD were negative.

A hemotologic study done after splenectomy revealed a hemoglobin level of 12.7 gm., hematocrit value of 35%, reticulocyte count of 2.7%, positive sickling preparations, and numerous target cells. Electrophoretic hemoglobin study (Tiselius method) showed 45% hemoglobin S and 55% hemoglobin C. The genealogy of the abnormal hemoglobins in the patient and her family is illustrated in the Chart; additional details are included in the report of Case 2.

Routine urinalysis was completely negative. A test of urinary diluting ability was normal, but urinary concentrating ability was depressed. Chest x-ray was negative.

Comment.—Patient 3 is a 14-year-old Negro girl with sickle-cell hemoglobin C disease and no ocular complaints. She is the sister of Patient 2. On a routine eye examination peripheral areas of chorioretinal atrophy were noted. Unlike the other two patients with sickle-cell hemoglobin C disease, she has had severe extraocular symptomatology secondary to sickle-cell disease, including jaundice, abdominal crises, joint and muscle pain, and recurrent splenic infarction—the latter necessitating a splenectomy at the age of 14. This observation is in keeping with the findings of Smith and Conley,[11] who have shown that sickle-cell hemoglobin C disease may run the gamut from a mild disease to one which parallels the clinical course of sickle-cell anemia in the severity of its manifestations.

Hyposthenuria was demonstrated in Cases 2 and 3 despite the lack of abnormal findings on routine urinalysis or a history of kidney trauma or disease. This selective impairment of the ability to concentrate urine has been demonstrated in other cases of sickle-cell hemoglobin C disease, the trait, and the anemia.[18] It has been suggested that subclinical intravascular sickling in the kidney may be the etiologic factor.

Study of the distribution of hemoglobin types in the three patients with sickle-cell hemoglobin C disease and their families (Chart) supports the concept that hemoglobins S, C, and A are controlled by allelic genes.[17,18] Neel et al.[19] have pointed out that

a pedigree of the type depicted in the Chart, *A*, is particularly valuable in proving allelism or close linkage. The idea that the rate of hemoglobin synthesis is also under genetic control [17] is strengthened by the presence of identical ratios of hemoglobins C and A in the two siblings of Case 1, with hemoglobin C trait, and almost identical ratios of hemoglobins S and C in Cases 2 and 3, who are brother and sister.

CASE 4.—A 34-year-old Negro man sustained an injury to his left brow in 1944. During the next five years he had repeated episodes of painless clouding of vision O. S. In 1949 he complained of eye pain for the first time. Examination at the Veterans' Administration Hospital, Indianapolis, revealed an aqueous flare, posterior synechiae, and a complicated cataract. The retina was difficult to visualize, but a dense white mass could be distinguished in the periphery. A diagnosis of atrophia bulbi, O. S., was made, and an enucleation was performed in December, 1949. The specimen was forwarded to the Armed Forces Institute of Pathology. Dr. Lorenz Zimmerman, of the Armed Forces Institute of Pathology, provided histologic sections, stained according to the hematoxylin-and-eosin, periodic acid-Schiff, Masson trichrome, and Van Gieson techniques, for study at the National Institutes of Health.

Cornea, sclera, and uveal tract were normal except for the presence of posterior synechiae. The anterior chamber contained pink-staining material in the hematoxylin-and-eosin-stained sections. There was a moderate amount of pigment trapped in the trabecular meshwork of the open angle. Remnants of the lens indicated the presence of a posterior cortical cataract with proliferation of nucleated elements in the involved area. The residues of an extensive vitreous hemorrhage and pigment-laden phagocytes occupied part of the anterior portion of the posteriorly detached vitreous.

The retina, which was the seat of the major pathological changes, was artificially detached by the formalin fixation, except for a slight degree of antemortem detachment indicated by a thin layer of subretinal transudate containing some migrated pigment epithelial cells. There was a massive gliosis affecting the inner layers of the retina around the optic nerve, which involved the entire temporal half of the retina up to the equatorial zone. A preretinal vascularized fibrous membrane blended with the glial proliferation and produced deep retinal folding near the nerve head (Figs. 10 and 11). At several sites hemorrhagic extravasates were located in the nerve, ganglion cell, and inner nuclear layers (Fig. 13). The outer layers of the retina were relatively well preserved except in the periphery, where gliosis and cystoid degeneration were present.

The lumina of dilated retinal vessels were filled with blood or, occasionally, with a homogeneous material. Other branches were partially obliterated (Fig. 11) and gave rise to neovascularization in the form of closely packed capillary tufts (Figs. 12 and 14). Some of the large vessels showed lymphocytic cuffing (Fig. 15). The red blood cells in the apparently congested vessels (Fig. 16) did not exhibit the sickling phenomenon to the same degree as the erythrocytes within the retinal hemorrhages (Fig. 13), in the thin layer of blood within the subretinal space, and in the hemorrhagic debris lying in the vitreous (Fig. 17).§

Since August, 1950, the patient has had several episodes of "smoky vision" O. D. with gradual clearing. On two occasions

§ The question of whether distortion of red blood cells by formalin fixation can mimic sickling or whether formalin itself increases the number of sickled forms has been dealt with recently by Mostofi, Vorder Bruegge, and Diggs.[20] They concluded that the sharp-pointed projections and crescent shapes of sickled red cells can be readily distinguished from the irregular forms and blunt projections of erythrocytes in formalin-fixed material. They add: "It is our belief that unless tissue is subjected to undue exposure to air before formalin fixation, the red blood cells, including the sickled ones, will be preserved in essentially unchanged form, and that any distortion will be on the side of decreased rather than increased prominence of the morphologic characteristics."

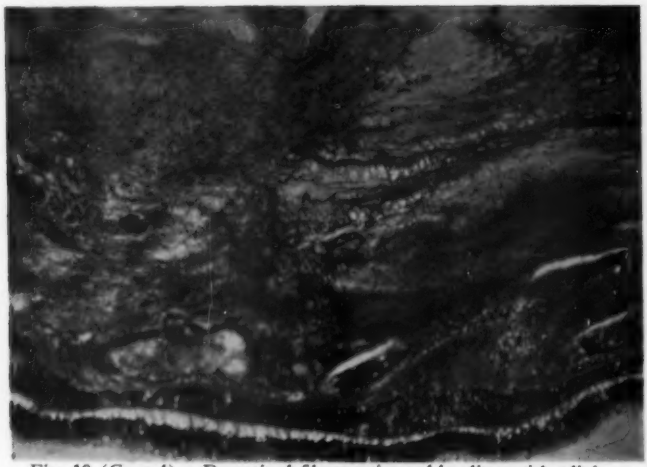


Fig. 10 (Case 4).—Preretinal fibrous tissue blending with glial proliferation in the peripapillary area of the retina. Masson's trichrome stain; reduced slightly from mag. × 80.

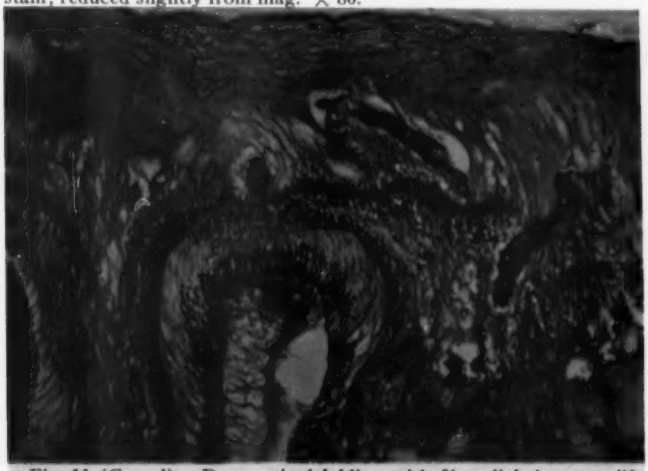


Fig. 11 (Case 4).—Deep retinal folding with fibroglial tissue proliferation and neovascularization around obliterated small vessels. Van Gieson stain; × 90.

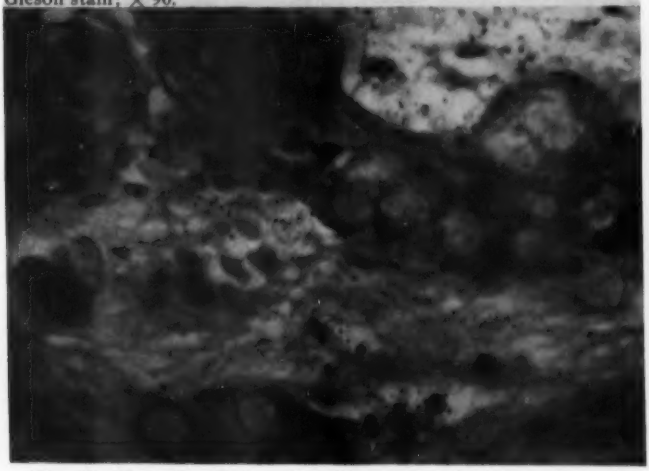


Fig. 12 (Case 4).—Tufts of proliferated capillaries in the retina. PAS stain; × 550.

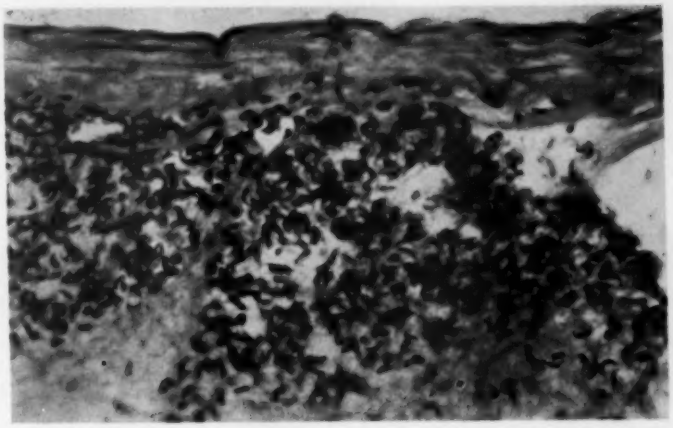


Fig. 13 (Case 4).—Sickled red cells in area of retinal hemorrhage. Van Gieson stain; reduced about 1/3 from mag. × 550.

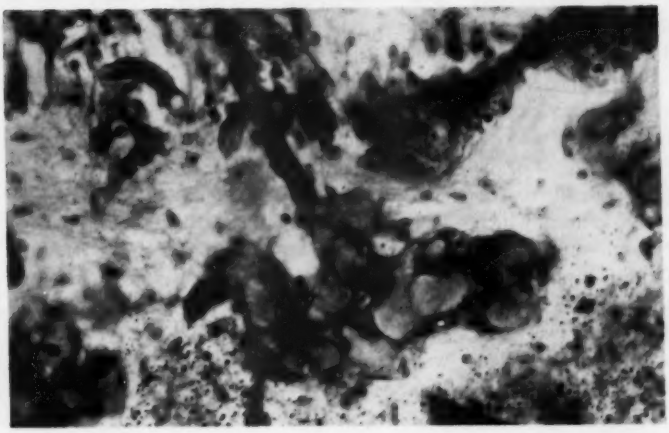


Fig. 14 (Case 4).—Newly formed retinal capillaries. PAS stain; reduced about 1/3 from mag. × 550.

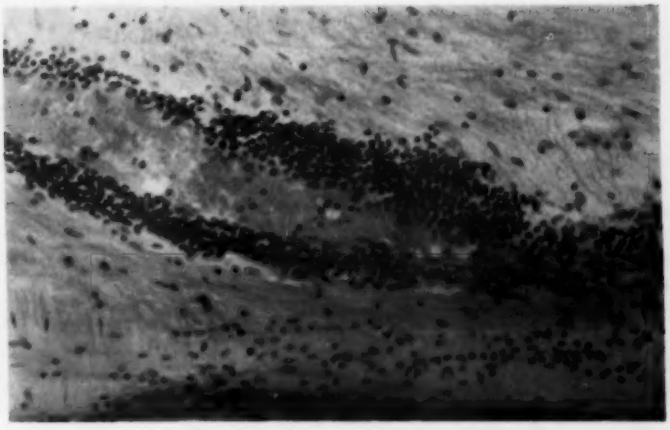


Fig. 15 (Case 4).—Lymphocytic cuffing of congested retinal vein. Hematoxylin and eosin stain; reduced about 1/3 from mag. × 350.

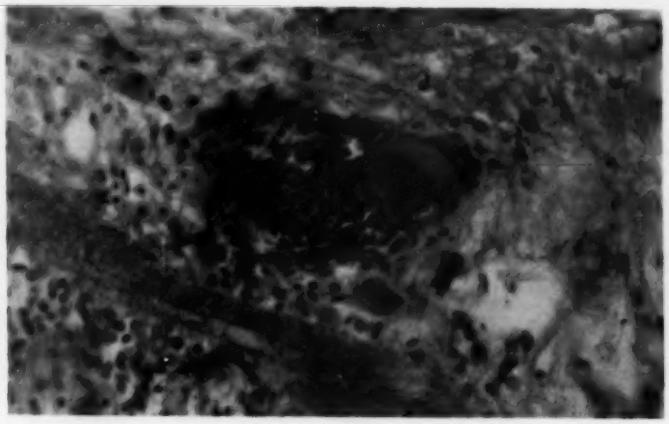


Fig. 16 (Case 4).—Congested retinal vein. Sickling less apparent than in retinal (Fig. 13) and vitreous (Fig. 17) hemorrhage. Van Gieson stain; reduced about 1/3 from mag. × 550.

when he was examined during these attacks definite evidence of vitreous hemorrhage was found. Grayish-white deposits were noted in the vitreous during an asymptomatic period, and these were considered to be the residua of previous vitreous hemorrhage. Fundus examination in 1950 showed several areas of glial-like proliferation in the retinal periphery with many small vessels at the summit of these white lesions, which were described as "aneurysmal" and "like a caput medusae." Perivasculitis and a disturbed vascular pattern preceded the lesions. An elevated and pigmented patch was seen inferiorly and was likened to a healed chorioretinitic focus. On reexamination, in 1957, visual acuity was 20/20, but there was a white glial-like flap in the inferior fundus periphery from 3 to 9 o'clock, perivascular sheathing of arterioles and venules, and the pigmented patch which had been noted previously.

The patient had an episode of jaundice in 1945, while stationed in the Phillipines, and several hospital admissions for an enlarged and painful spleen. Marked splenomegaly has persisted to the present.

In 1952, following a year of employment as an attendant in a tuberculosis isolation ward, active pulmonary tuberculosis was discovered. Chest x-rays prior to 1952 were reviewed and found to be normal, and there was no family history of tuberculosis. It is important to note that the patient's exposure to tuberculosis, and evidence of active infection, occurred several years after ocular

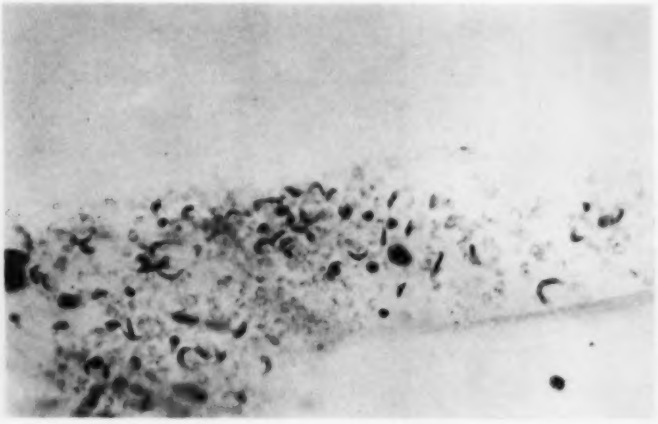


Fig. 17 (Case 4).—Sickled red cells in absorbing hemorrhage in anterior part of vitreous. Van Gieson stain; reduced about 1/3 from mag. × 550.

pathology was noted in either eye. This fact, in addition to the lack of tuberculoid lesions in the histologic sections of the left eye and the similarity of the fundus lesions in the right eye to those in other cases of sickle-cell disease, is sufficient to eliminate consideration of tuberculosis as the etiologic factor in this patient's eye disease.

The presence of a sickling tendency was known for many years. The patient was diagnosed as having sickle-cell trait or anemia during his hospitalizations. He is listed as Case 3 in the report of Henry and Chapman [30] and was classified by them as having sickle-cell anemia. Hemoglobin electrophoresis was performed on the patient's blood at the National Institutes of Health in February, 1957, and both sickle-cell hemoglobin (55%) and hemoglobin C (45%) were found. This clearly established a diagnosis of sickle-cell hemoglobin C disease.

Hematologic studies have been performed many times during the patient's hospitalizations. Hemoglobin values were 13 to 14 gm.; reticulocyte counts, about 1%, and target cells have always been numerous. Bleeding, coagulation, and prothrombin times have been normal on all occasions. Erythrocyte fragility was moderately decreased.

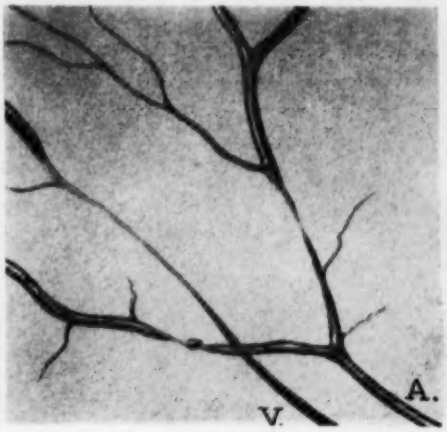
A urine concentration test in 1952 showed a specific gravity not exceeding 1.015, but a urine dilution test was normal. Routine urinalyses were normal except for one episode of pyuria and specific gravities which were consistently below 1.015.

Comment.—The patient is a 34-year-old Negro man with a diagnosis of sickle-cell hemoglobin C disease. His left eye was enucleated in 1949, after five years of "recurrent blindness" (probably repeated vitreous hemorrhages), which is said to have begun after a blow to the left brow. Pathologic examination showed a complicated cataract, sickled erythrocytes in the vitreous, and retinal changes including gliosis, a preretinal fibrous membrane, new vessel formation, obliterated vessels, retinal hemorrhage, and perivascular round-cell cuffing. Since 1950 there have been repeated episodes of spontaneous vitreous hemorrhage in the right eye, followed by gradual clearing. On examination of this eye in 1950 and 1957 glial proliferation and vascular changes were noted similar to those found in Cases 1 and 2 of this study.

The extraocular manifestations of sickle-cell disease in this patient include decreased urinary concentrating ability, a finding noted in all the patients of this series, and splenomegaly, a finding prominent in many cases of sickle-cell hemoglobin C disease.[11]

CASE 5.—An 18-year-old Negro woman with known sickle-cell disease noted blurring of vision in the left eye while she was in active labor on Nov. 28, 1956, at District of Columbia General Hospital. (The patient had been followed carefully in prenatal clinic with monthly urinalyses and blood pressure determinations, and there was no sign or symptom of toxemia of pregnancy). Following delivery of a viable premature baby one day later, she informed the obstetrician of her visual difficulties. Ophthalmologic examination revealed an exudative elevation and edema of the retina at the posterior pole, with scattered retinal hemorrhages throughout the periphery of the fundus, and one preretinal hemorrhage ad-

Fig. 18 (Case 5).—Superior nasal retina, O. S. Focal narrowing of the blood column in an arteriole and venule one week after onset of symptoms. Several days later these vessels appeared normal.



jacent to the macula O. S. Examination a week later disclosed fading of the hemorrhages and irregular narrowing, dilatation, and interruption of the blood column in arterioles and venules (Fig. 18). Arterial and venous pulsations on the optic disk could be elicited with digital pressure.

Since the age of 4 years the patient has had innumerable attacks of severe arthralgias, muscle pain, and anemia, with frequent hospitalizations for blood transfusions. There have also been several episodes of "pneumonia," which were suggestive of in situ pulmonary infarction. Urinary specific gravity has never exceeded 1.016 in over 20 hospital admissions, and there have been several attacks of acute pyelonephritis.

During this pregnancy the patient denied the occurrence of sickle-cell crises. She was compensated at a hemoglobin level of 7 to 8 gm. and had not required transfusions for over a year. For the two months prior to delivery, and during her postpartum course, she received a vasodilating drug (nylidrin [Arlidin], 24 mg. daily) to aid in preventing obstructive vascular complications.

The patient was admitted to the Ophthalmology Branch of the National Institutes of Health on Dec. 12, 1956, for study of retinal pathology in the left eye presumed to be secondary to sickle-cell disease.

Physical Examination.—Visual acuity in the right eye was correctible to 20/20. External and internal examinations were normal.

Vision in the left eye was finger counting at 1 ft. There were no abnormalities on external examination and biomicroscopy of the anterior segment. Fundus examination disclosed edema of the macular area extending nasally to the optic disk. A preretinal hemorrhage was still present in this area, but the retinal hemorrhages had almost disappeared. Though arterial pulsations could be elicited in the arteries on the optic disk, the caliber of veins and arteries emerging from the disk was smaller than in the right eye.

There were localized constrictions and dilatations of arterioles and venules throughout the temporal retina (Fig. 19) and in the venules of the nasal retina beginning in the preequatorial region and extending peripherally. The blood column in these involved vessels ranged from a normal deep red color to areas of light pink and pale white. In the pink-colored segments there was a granular appearance produced by clusters of erythrocytes which showed no movement.

Visual field examination with a 10 mm. white target at 330 mm. showed retention of a 50-degree segment of temporal field, beginning at the optic disk. The remainder of

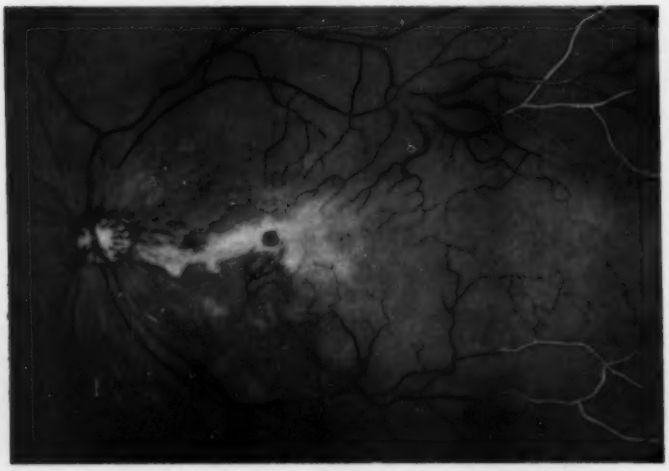


Fig. 19 (Case 5).—Posterior pole and temporal retina, O. S. Hyperemia of the disk and edema in the macular area are associated with multiple constrictions and dilatations of the blood column in arterioles and venules. The beginning of the chalk-white appearance of vessels in the temporal retina is visible.

the temporal field and almost the entire nasal field were lost under these conditions of testing. These visual field findings suggested retinal dysfunction in the nasal periphery and throughout the temporal retina—the areas where vascular abnormalities were noted on ophthalmoscopy.

Diagnostic Studies.—The white blood cell count was 13,700, with a normal differential count. The red blood cell count was 3,360,000; the hemoglobin was 6.9 gm., and the hematocrit value was 25%. Red blood cell indices showed a mean corpuscular volume of 74 cu. μ, a mean corpuscular hemoglobin of 20$\mu\gamma$, and a mean corpuscular hemoglobin concentration of 28%. Serum iron was 65 mg. per 100 cc. The reticulocyte count was 6.9%. A sickling preparation was immediately positive.

Hemoglobin electrophoresis revealed over 99% of a component with the same electrophoretic mobility as sickle-cell hemoglobin and an insignificant amount of fetal hemoglobin. Hemoglobin solubility studies disclosed a higher solubility than is usually found in cases of sickle-cell anemia, with low proportions of fetal hemoglobin. The electrophoretic and solubility studies suggested the presence of sickle-cell hemoglobin D disease. However, microcytosis and such low levels of fetal hemoglobin have not been reported in this condition. Furthermore, the diagnosis could not be confirmed by familial hemoglobin studies, since the patient's father was unavailable for study. Investigation of the patient's mother revealed sickle-cell hemoglobin and normal hemoglobin, i. e., sickle-cell trait.

Bleeding time, coagulation time, platelet count, and prothrombin time were normal. Serum calcium was 10.1 mg. per 100 cc. Cephalin flocculation test was negative; serum bilirubin was 0.7 mg. per 100 cc., and serum cholesterol was 185 mg. per 100 cc. Blood urea nitrogen was 11 mg. per 100 cc. A catheterized urine specimen showed a specific gravity of 1.014 and no albumin, sugar, cells, or casts.

X-ray of the skull revealed no abnormalities. Chest x-ray disclosed an enlargement of the heart in its transverse diameter; this was believed to be consistent with mild cardiac enlargement on the basis of anemia.

Course.—There was a gradual decrease in edema at the posterior pole, with an increase in visual acuity from finger counting at 1 ft. to finger counting at 3 ft. The venules and arterioles in the temporal retina and the peripheral portions of the venules in the nasal retina became chalk-white within several days (Fig. 20). A few stationary clusters of erythrocytes appeared as light-pink areas within the white vascular tree. By the time of discharge, one week later, even the delicate capillary-like vascular arcades, which are ordinarily invisible on ophthalmoscopy, were easily discernible as a white latticework in the temporal retina (Fig. 21). Three months later the white material was present only in isolated segments of vessels. The arterioles and venules which had previously appeared chalk-white were attenuated and barely discernible except where a pale gray vascular sheathing outlined their course. Adjacent to the sheathed and obstructed vessels delicate tortuous newformed vessels were now apparent.

Fig. 20 (Case 5).—Temporal retina, O. S. Fundus photograph of the chalk-white vessels which developed in an area of stasis. The smallest retinal vessels appear as fine anastomosing white lines in the background.

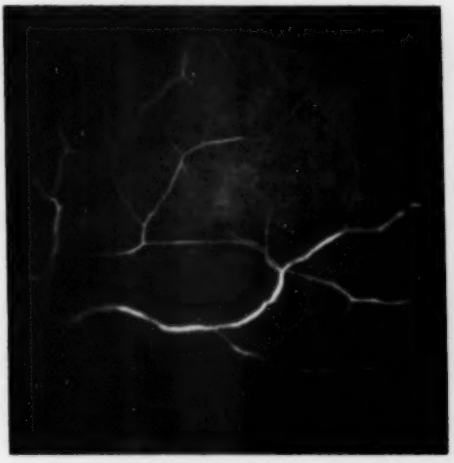


Fig. 21 (Case 5).—Temporal retina, O. S. A sketch of the white appearance of the finest retinal vessels. This delicate white lattice-work was present throughout the temporal retina and in the nasal periphery distal to obstructed vessels.

Comment.—An 18-year-old Negro girl with sickle-cell disease, during active labor, several hours before delivery of a premature baby, noted a marked reduction of vision in the left eye. Subsequent examinations revealed an atypical picture of stasis and obstruction in the retinal vascular bed, with secondary retinal edema and visual field loss.

Hemoglobin electrophoresis and solubility studies demonstrated the presence of sickle-cell hemoglobin and another abnormal hemoglobin of similar electrophoretic mobility, suggesting sickle-cell hemoglobin D disease. The extraocular symptomatology related to sickle-cell disease in this patient resembled the severe manifestations noted in sickle-cell anemia. Hemolytic crises and episodes of joint and muscle pain necessitated repeated hospitalizations from early childhood. A diagnosis of in situ pulmonary infarction was made on two occasions when the patient was admitted with "pneumonia"; this complication of sickle-cell disease is being found with increasing frequency.[21] Hyposthenuria was present, as in all other patients in this study. The repeated attacks of pyelonephritis may also have been a reflection of sickle-cell renal involvement, since the incidence of pyelonephritis is reported to be increased in all types of kidney disorders,[16] and this has been noted as well in sickle-cell disease.[22]

General Comment

1. *Ocular Findings.*—The ocular changes in the five patients with sickle-cell disease presented in this study were predominantly vascular in nature, involving retina, optic disk, and conjunctiva. Retinal, preretinal, or vitreous hemorrhage occurred in four patients.

The retinal pathology in the four patients with sickle-cell hemoglobin C disease comprised a variety of lesions, usually peripheral in location, with a predilection for the temporal retina. Single and multiple patches of retinitis proliferans were present in two patients (Figs. 1 and 7). Tortuous and anastomosing venules and arterioles were associated with the proliferating glial or fibrous tissue masses at their borders, on

their surface, or beneath. In other areas of arborizing retinal vessels glial tissue was completely absent or confined to a fine veil (Figs. 3 to 5 and 8).

A loose anastomosing vascular network was seen in Case 2, derived from arterioles and venules (Fig. 8). Dense circumscribed networks in Case 1 were notable for the presence of multiple saccular and varicose aneurysms (Figs. 3 to 5); in those areas where venous and arterial tributaries could be separated, the aneurysms, and the major portion of the arborization, appeared to originate from the venous side. The evolution of a vascular network could be followed in Case 1 (Figs. 4 and 5). First, there were fine vascular tufts adjacent to an irregularly branching venule. These vessels, and a neighboring arteriole, then became incorporated into a single arborizing unit in which aneurysmal dilatations were prominent.

Retinal aneurysms were noted in two areas of localized venous pathology at the point where looping of a vessel occurred (Case 1). In one instance the vascular loops projected into the vitreous from a dilated venous channel and the aneurysms occurred as terminal bulbous dilatations within the vitreous (Fig. 2). Varicose and saccular aneurysms were also seen in a vascular loop lying in or on the retina, which had developed from the fine branches of a peripheral venue. Other changes present in both arterioles and venules included beading, sheathing, tortuosity, abrupt terminations of the blood column, and the development of twisted vascular tufts adjacent to such areas of pathology. The chalk-white appearance of vessels distal to obstructions, as noted in Case 2, will be discussed in connection with similar changes in Case 5.

Peripheral areas of pigmentary change in two subjects were characterized by a scalloped gray border (Fig. 9); they were interpreted as chorioretinal atrophic changes. Pigmented circumscribed lesions, similar to focal areas of healed chorioretinitis, were also observed.

The appearance of punctate red spots on the optic disk of Case 2 suggested pinpoint saccular aneurysms or the end-on view of proliferating vessels. Several months later a network of fine small blood vessels was evident on the disk in this region.

Conjunctival changes in the first cases consisted of sausage-like dilatation of fine vessels, with red blood cells massed in the dilated segments; saccular microaneurysms were discovered in Case 1 (Fig. 6). A comparative study of normal patients and those with sickle-cell disease will be necessary to validate the significance of these observations, because of the well-known variability in configuration of conjunctival vessels in normal subjects.

A distinctive finding in two cases was the presence of preretinal hemorrhages in the temporal periphery, simulating retinal tears. This was first noted by one of us (M. G. H.) in a patient with sickle-cell retinopathy not included in this study. The major points of resemblance between the hemorrhage in its early stages and retinal tears were as follows: the luminous red color, which was also apparent in the intraretinal hemorrhages of Case 5; sharp ragged borders, without the formation of a horizontal upper edge characteristic of preretinal hemorrhages; the thinness of the hemorrhagic layer and its close proximity to the retinal surface, which accounted for the lack of elevation and absence of shadow cast on the retina. Subsequently, these red patches could be differentiated from retinal tears by their mobility, fragmentation, and disappearance or their transformation into grayish-white vitreous deposits.

The histologic findings in Case 4 complemented the clinical observations in this patient's second eye and in the other cases of sickle-cell hemoglobin C disease. There was new vessel formation, a fibrous vascular membrane on the surface of the retina, obliterated vessels, and preretinal and vitreous hemorrhage in which sickled cells could be seen. Among the interesting facts derived from the histologic examination were

the presence of both fibrous and glial elements in the areas of retinitis proliferans and the higher percentage of sickled cells noted in the vitreous, where oxygen tension is lowest, as compared with the lesser degree of sickling intravascularly. However, no significant difference could be found between the number of sickled cells in the arterioles and in the venules. It is doubtful whether the perivascular round-cell infiltration played a significant role in the development of the retinopathy in view of the small number of involved vessels.

The fundus pathology in Case 5 was acute in onset and consisted of retinal edema extending from the optic disk to the macular area, retinal and preretinal hemorrhages, and narrowing, dilatations, focal constrictions, and interruptions of the blood column in arterioles and venules (Figs. 18 and 19). This was not a central retinal artery obstruction, since arterial pulsation could be elicited on the disk, the edema was restricted to a small area of fundus, and venous pathology predominated. Central venous obstruction could also be excluded, since venous tortuosity was absent, venous dilation was present only in scattered segments of venules distal to constrictions, and hemorrhages were minimal. Though the exact nature of the obstructive vascular process in this patient was uncertain, the focal involvement of vessels in all quadrants suggested multiple lesions due to vasospasm or intravascular obstructions.

One week after the onset of symptoms the blood column in the areas of vascular pathology showed pink segments in which stationary clusters of erythrocytes could be distinguished. There was a gradual transformation from pink to white within the next week so that a large portion of the retinal vascular bed became chalk-white (Figs. 19 to 21), followed by partial disappearance of this whiteness during the next three months. The short period of time in which these changes appeared and disappeared indicated that they were due to abnormalities occurring in the intraluminal contents rather than in the vessel wall. Similar changes in vessel color developed in the right eye of Case 2.

The possibility that this stark white appearance of the blood column might be related to abnormalities of calcium or lipids was investigated in Case 5. Blood cholesterol levels were normal, and inspection of the patient's serum showed no evidence of hyperlipemia. There was no elevation of blood calcium; orbital tomograms disclosed no evidence of calcification within the eye, and x-rays did not show abnormal calcification elsewhere in the body. Another consideration was that the white contents represented blood devoid of hemoglobin, as it might occur if there was a separation of serum from cells in an area of stasis or if severe hemolysis had developed. The latter explanation was suggested by Dr. Ben Fine, of the Armed Forces Institute of Pathology, and is based on the fact that sickling is enhanced by the decreased oxygenation and accumulation of acid metabolites which develop after vascular obstruction and the sickled cells which result can be rapidly hemolyzed.[23] Fine[24] demonstrated that increasing degrees of in vitro hemolysis of normal or sickled red blood cells produced a residue of hemolyzed cells varying in color from crimson to pure white. Electron microscopy confirmed the fact that the white material consisted of masses of fragmented erythrocyte membranes devoid of hemoglobin. These experiments support the idea that the white appearance of intravascular contents in some patients with sickle-cell disease may be due to the hemolysis of sickled erythrocytes in areas of stasis.

The ocular changes in sickle-cell disease reported in the literature, exclusive of scleral and conjunctival icterus, are listed in Table 2. They include vitreous hemorrhage[11,27,30,32] retinitis proliferans,[30] aneurysmal vascular dilatations,[27,32] and peripheral chorioretinal atrophy,[30] all of which were noted in the present study. Certain of these findings deserve special mention related to observa-

TABLE 2.—*Review of Literature*

Reference	Diagnosis	Electrophoretic Confirmation	Cases Examined, No.	Cases with Ocular Pathology, No.	Type of Ocular Pathology (Cases, No.)
Harden (1937) [24]	Anemia	No	2	2	Dilated and tortuous veins; lesser dilatation of arteries (2)
Klinefelter (1942) [24]	Anemia	No	12	7	Tortuous veins (7)
Henderson (1950) [13]	Anemia	No	54	1	Retinal hemorrhage (1)
Edington & Sarkies (1952) [27]	S-C disease	Yes *	2	2	Retinal microaneurysms (2) Retinal hemorrhage (1) Vitreous hemorrhage (1)
Rudd, Evans, & Peeney (1953) [28]	S-C disease or S-thalassemia	No †	1	1	Retinal and vitreous hemorrhage and exudation (1)
Henry & Chapman (1954) [30]	Anemia	No ‡	10	5	Retinal hemorrhage (2) Vitreous hemorrhage (2) Retinitis proliferans (2) Chorioretinal atrophy (3) Tortuous veins (1)
	Trait	No ‡	19	4	Retinal hemorrhage (3) Vitreous hemorrhage (1) Glial proliferation (2) Chorioretinal atrophy (1) Retinal detachment (1)
Smith & Conley (1954) [11]	Anemia	Yes	15	14	Tortuous veins (14)
	S-thalassemia	Yes	4	1	Tortuous veins (1)
	S-C disease	Yes	16	5	Tortuous veins (2) Vitreous hemorrhages (3) Retinal aneurysmal dilatations (1)
Kubakow, Weimokly, & Lyons (1955) [31]	Trait §	Yes	1	1	Bilateral central retinal artery occlusion (1)
Hannon (1956) [32] #	Anemia	Some	53	25	Dilated and tortuous veins (25)
	Trait	Some	62	1	Dilated and tortuous veins (1)
	S-C disease	Yes	20	7	Vitreous hemorrhage Occlusions of terminal arterioles and venules Anastomosing vascular networks and twisted venules with terminal dilatations extending into the vitreous

* Both cases were originally classified as the anemia. Electrophoretic study later demonstrated sickle-cell hemoglobin C disease in the first case. [24] The absence of anemia, presence of 75% target cells, marked splenomegaly, and the high incidence of hemoglobin C in the region of Africa from which this patient came strongly implicate sickle-cell hemoglobin C disease in the second case.

† This case was reported as thalassemia minor with sickling in a West African Negro, but the hematologic findings are also consistent with sickle-cell hemoglobin C disease. Hemoglobin electrophoresis would be required to establish the correct diagnosis. The high incidence of hemoglobin C in West Africans is in favor of sickle-cell hemoglobin C disease.

‡ The authors state that electrophoretic studies were performed in a few of these cases. Since no details are given, it is uncertain whether such testing was done to confirm the diagnosis in any of the patients who demonstrated ocular changes. Recently, Case 3 of their paper was investigated electrophoretically and sickle-cell hemoglobin C disease was demonstrated (see Case 4 of the present study).

§ Active pulmonary tuberculosis and systemic lupus erythematosus were also present in this patient.

This study includes case material reported by Smith and Conley. [11]

tions in the four patients with sickle-cell hemoglobin C disease.

The multiple areas of glial proliferation and vascular tortuosity in Case 1 (Fig. 1) parallel the appearance and location of similar lesions in a patient with sickle-cell anemia reported by Henry and Chapman [30]; the fundus drawings are strikingly similar. Two other patients in their series also showed multiple localized areas of glial proliferation. The microaneurysms noted by Edington and Sarkies [27] occurred in the course of, or adjacent to, peripheral venules, and a similar association between microaneurysms and venules was frequently seen in this study. Hannon,[32] in his important contribution to the diagnosis of sickle-cell retinopathy, described arborizing vascular networks in relation to venules, terminal dilatations of twisted venules projecting into the vitreous, multiple occlusions of peripheral venules and arterioles, and vitreous hemorrhage in patients with sickle-cell hemoglobin C disease.‖ These changes, and their tend-

‖ The patient presented as Case 3 by Hannon was hospitalized at the National Institutes of Health in February, 1957, for recurrent vitreous hemorrhages O. D. At the time of Hannon's last examination, in March, 1956, there was a massive vitreous hemorrhage present O. S. and vascular abnormalities and retinal hemorrhage O. D., with a salmon-pink exudative plaque in the temporal periphery O. D. Scleral diathermy to the right eye was recommended, but it was refused by the patient. Examination at the N. I. H. in February, 1957, revealed a dense cataract O. S., preretinal and vitreous hemorrhages O. D., and a zone of glial proliferation from 8 to 11 o'clock O. D. The hemorrhage in the vitreous was observed to undergo changes from red, to pink, to a grayish-white cottony substance, as noted in Case 1 of this study. It is probable that the exudative salmon-pink mass

(*Footnote continued on following page*)

ency to begin in peripheral temporal quadrants, were also noted in the present study.

The findings in the four patients with sickle-cell hemoglobin C disease thus reflect the full range of retinal pathology previously described in sickle-cell disease and serve as an additional confirmation of sickle-cell retinopathy as a distinct clinical entity. Observations as yet unreported in other studies include preretinal hemorrhages simulating retinal tears, neovascularization and microaneurysm formation on the optic disk, areas of rete mirabile in which both arterioles and venules participate, vessels appearing chalk-white owing to changes in their contents, and conjunctival vascular abnormalities.

2. *Relation to Pathophysiology of Sickle-Cell Disease.*—The pathologic manifestations of sickle-cell disease have been related to the properties of the abnormal sickle-cell hemoglobin.[23] Under conditions of lowered oxygen tension this hemoglobin aggregates and the red blood cells assume a distorted shape. The sickled cell lacks the easy flexibility of normal erythrocytes; its rigidity and abnormal shape may lead to blockage of terminal capillaries.[33] There is also a definite increase in viscosity of sickled blood which is attributed to the enmeshing and interlocking of the sickled erythrocytes. This change in viscosity is part of a cycle in which stasis, decreased pH, and continued tissue oxygen uptake increase the sickling and stasis. The viscous conglomerates which develop in the small vessels of the body may lead to obstruction and infarction, which frequently occur without the formation of true vascular thrombi.[34] Bauer[35] has suggested that there is no other pathologic process in which stasis and impaction of erythrocytes occur to the same degree as in sickle-cell disease.

Since a multitude of physiologic factors may affect the sickling process, it is difficult to assess the vulnerability of a given organ to sickle-cell pathology. Nonetheless, it is interesting to note that the retina possesses a high rate of glycolysis,[36] which favors a rapid depletion of oxygen from circulating red blood cells. This may be an important factor in the precipitation or augmentation of sickling within the retinal capillary bed. Furthermore, the presence of an end-arteriole system in the retina predisposes to anoxia and tissue damage once blockage occurs.

Stasis and obstruction of small vessels are the common pathologic denominators of sickle-cell disease in many organs.[33-35,37-39] They are reflected in the ocular findings of tortuosity, segmentation, multiple obstructions, obliteration, and sheathing of retinal arterioles and venules. The presence of varicose and saccular aneurysms noted in the present study may also be linked to vascular stasis; they have been observed both ophthalmoscopically and histologically in central retinal vein occlusion and following experimental blockage of the central retinal vein in cats.[40]

Ditzel and White[41] have recently summarized the evidence which suggests that the major etiologic factor in the production of diabetic retinopathy is venous stasis. They have pointed out certain basic similarities between the retinopathy in diabetes and central venous occlusion, such as microaneurysm formation, retinitis proliferans, vitreous hemorrhage, venous abnormalities in conjunctiva and retina, and the development of vascular networks along the retinal surface and projecting into the vitreous. It is significant that similar changes are also dominant in the fundus picture of sickle-cell disease, where venous stasis is probably an

described by Hannon represented a stage in the transformation of a vitreous hemorrhage. The preretinal hemorrhages exhibited the same close resemblance to retinal tears described in two other patients in this report. While the patient was under observation a massive spontaneous vitreous hemorrhage occurred in the right eye which obscured all fundus details and left the patient with light perception only. In assessing the tendency to vitreous hemorrhage in this patient, it should be noted that an unexplained thrombocytopenia and elevated prothrombin time were present, in addition to the sickle-cell retinopathy. This patient was referred for study from the National Naval Medical Center, Bethesda, Md.

important etiologic factor. This is also consistent with the observations of Wise[42a] that microaneurysms and retinal vascular networks (the latter representing neovascularization or a dilation of preexisting vascular channels) are frequent findings in a wide variety of retinopathies where venous and capillary blockage occur.* However, in the present investigation it was frequently observed that vascular networks and microaneurysms developed distal to obstructed arterioles, as well as venules. Similar findings were described by Ashton[43] in studies of arteriolar involvement in diabetic retinopathy. Such observations suggest that there is still much to be learned about the interplay of arterial and venous pathology in retinal vascular disorders. Postmortem injection studies of the choroidal and retinal vasculature in patients with sickle-cell disease would be of value in elucidating this problem.

Hemorrhage is a serious complication of sickle-cell retinopathy. It is presumably secondary to the vascular changes, since bleeding tendencies due to hematologic abnormalities are not characteristic of sickle-cell disease and they have been specifically ruled out in the four patients of this study with intraocular hemorrhage. Edington and Sarkies[27] noted retinal hemorrhage adjacent to a microaneurysm, and Hannon[32] proposed that the site of bleeding in his patients was terminally dilated vessels projecting into the vitreous. Such vascular pathology, which has also been noted in this study, probably develops after stasis and obstruction of some duration. The occurrence of hemorrhages in Case 5, prior to the development of aneurysms and neovascularization, may be related to the acuteness of the vascular obstructions.

3. *Correlation with Genotypic Forms of Sickle-Cell Disease.*—The correlation of retinal pathology with the different genotypic forms of sickle-cell disease must be based on studies which fulfill two criteria: (1) ocular examination by an ophthalmologist, through a maximally dilated pupil, to ensure visualization of peripheral lesions and recognition of early changes; (2) adequate hematologic investigation, including routine hemoglobin electrophoresis, to identify correctly the type of sickle-cell disease. (Hemoglobin solubility and familial studies may be necessary in problem cases.)

None of the studies which report ocular changes in a series of patients with sickle-cell disease fulfill these two criteria. Henry and Chapman[30] state that electrophoretic studies were obtained in a few of their patients, but these are not identified. Klinefelter[26] and Henderson[12] completed their studies prior to the use of hemoglobin electrophoresis; in addition, Henderson's report of ocular pathology was restricted to a case in which retinal hemorrhage was the presenting symptom, but there is no mention of ophthalmoscopic examination of the patients without ocular complaints. The series of normal ocular findings in sickle-cell trait, anemia, and some of the cases of sickle-cell hemoglobin C disease reported by Conley and Smith[11] and Hannon[32] suggests reevaluation, since study of the eye findings in most of these patients was based upon a review of hospital records, rather than a systematic fundus examination in each case by the same investigators. Furthermore, the majority of cases in Hannon's series which were classified as sickle-cell trait or anemia had not been confirmed electrophoretically.

The small number of reported cases of sickle-cell retinopathy, as well as the inadequacies in ophthalmologic and/or hematologic examination of these patients, make it impossible to reach any conclusion regarding the incidence of ocular change in the different types of sickle-cell disease. However, certain trends have been noted which are worthy of mention.

Retinal vascular tortuosity has been seen frequently in sickle-cell anemia,[32] but significant retinopathy or hemorrhage has not

* A detailed discussion of the observations of George Wise[42a] is included in his comprehensive study of retinal neovascularization published in the *Transactions of the American Ophthalmological Society*, 1956.[42]

yet been reported in an electrophoretically proven case. Though vascular tortuosity is less frequent in sickle-cell trait,[32] there are two cases in which a retinopathy was observed in electrophoretically confirmed cases. Clifford and Tanaka [44] noted vitreous hemorrhage and retinal microaneurysms in a 39-year-old Negro man with sickle-cell trait in whom extensive investigation revealed no other systemic or hematologic abnormalities. Kabakow, Van Wiemokly, and Lyons [31] described bilateral central retinal artery occlusion in a 36-year-old Negro woman with sickle-cell trait, active pulmonary tuberculosis, and systemic lupus erythematosus. The latter investigators considered the possibility that sickled cells might have precipitated the arterial occlusions, but they concluded that this was unlikely because there had been no accounts of obstructive vascular disease in patients with sickle-cell trait except for splenic infarctions,[45] and here an unphysiologic hypoxic stimulus—high-altitude flying—was always the precipitating factor. However, there have been several recent reports of active sickle-cell symptomatology and pathology in patients with electrophoretically proven sickle-cell trait, including hemolytic episodes,[46-48] gross hematuria,[15] and bowel and cerebral infarctions,[49] without a history of high altitude flying. Such findings suggest that sickle-cell trait may no longer be considered a clinically benign carrier state and may be incriminated in the development of hemolysis and vascular occlusions. Nonetheless, in the patient reported by Kabakow et al.[31] the presence of several concomitant disease processes makes it impossible to reach a definite conclusion as to the role played by the sickle-cell trait in the development of the retinal arterial obstructions.

Sickle-cell hemoglobin C disease has been found in all the previous reports of retinopathy in electrophoretically studied cases of sickle-cell disease [11,27,32] and in four of five patients in the present study. Conley and Smith [11] have described other complications of sickle-cell disease which were noted more frequently in patients with sickle-cell hemoglobin C disease than with the anemia. These comprised aseptic necrosis of the femur, hemolytic crises and mortality during pregnancy, and gross renal hematuria. Since the clinical course and manifestations of sickle-cell anemia are usually more severe than in its genetic variants, the apparent prominence of these complications in the latter cases in surprising. Confirmation must await the comparative study of larger groups of patients and the assessment of factors such as age, total hemoglobin concentration, and percentage of sickle-cell hemoglobin as to their bearing on the general and local manifestations of the entities comprising sickle-cell disease. However, the possibility that hemoglobin C may also predispose to vascular obstruction must be considered, in view of a report of multiple pulmonary arterial thrombi in a postmortem examination of a patient with homozygous hemoglobin C disease.[50] The explanation for this unexpected finding is unknown.

4. *Ophthalmologic Significance.*—The recognition that acute obstructive vascular episodes and chronic obstructive vascular disease with secondary vitreous hemorrhage may develop on the basis of sickle-cell disease is of importance for the clinical ophthalmologist. Such pathology occurring in Negroes or in Causacians of Mediterranean origin (i. e., Italians, Greeks, and Turks) should be investigated by means of the standard sodium metabisulfate test for demonstration of a sickling tendency, with electrophoretic studies reserved for those patients with positive sickling preparations. This is particularly important in patients who have been diagnosed as having Eales' disease, a poorly defined clinical syndrome consisting of recurrent retinal and/or vitreous hemorrhages in young adults. Though the diagnosis of sickle-cell retinopathy brings with it no specific therapy for the underlying hemoglobin disorder at the present time, its importance in preventing the host of medical treatments commonly used for Eales' disease is obvious. Furthermore, as in Case 1, the ocular changes may be

the first clue to the presence of a hematologic disorder with protean symptomatology.

It is probable that in some instances systemic or ocular disease may be factors in precipitating retinal vascular occlusive complications in sickle-cell patients. Systemic infections in patients with sickle-cell disease are known to precipitate generalized sickle-cell crises; it is reasonable to assume that localized infections might have similar sequelae within the affected organ. Inflammation, trauma, or degenerative changes often induce anatomic alterations in vessels, vasomotor phenomena, or a tendency to blood sludging [51]—the latter being a fundamental type of biologic response to infection and tissue damage. Such events could trigger a vicious cycle of stasis, hypoxemia, and sickling and result in ocular pathology. Therefore, the presence of other diseases and abnormalities in patients with a sickling tendency suggests caution in attributing their ocular changes solely to the hemoglobinopathy.

Hannon [32] has suggested the use of surface diathermy for the type of sickle-cell retinopathy associated with vitreous hemorrhage, in order to obliterate the involved vessels which are presumed to be the source of hemorrhage. The peripheral location of most of these lesions makes such a procedure technically feasible. The tendency of the vascular changes to extend to all quadrants may make it necessary to diathermize the entire circumference of the eye, thus necessitating more than one operation. Such extensive diathermy has been done successfully by Verhoeff [52] and Franceschetti [53] in patients with Eales' disease.

Hannon chose for operation patients with vascular retinopathy in one eye in whom massive vitreous hemorrhage had reduced vision to light perception only in the other eye. The logic of this approach is reflected in the course of Case 3 in Hannon's study, who fits into this category but refused diathermy to the better eye. As noted elsewhere in the present study, this patient subsequently developed a massive vitreous hemorrhage in his "good" eye and now retains only light perception in each eye. However, any attempt to extend the indication for surgery to patients with vascular changes in one or both eyes without evidence of massive hemorrhage would appear to be premature at the present time. The incidence of vitreous hemorrhage in patients with sickle-cell vascular retinopathy and the number of years that vascular changes may precede the hemorrhage are unknown. Furthermore, Cases 1 and 4 of this study have been examined four and seven years, respectively, after the onset of recurrent symptomatic vitreous hemorrhage and still maintain normal vision. Until more information is available concerning the natural history of sickle-cell retinopathy, the conservative course proposed by Hannon is to be recommended.

As a pathologic entity sickle-cell disease is mainly an affection of the small blood vessels. Turner and Bowers [54] have reemphasized the fact that such vascular lesions may give few clinical manifestations unless the vessels are visible, as in retina and skin, or their presence results in laboratory findings, as in kidney disease. The pertinence of their remarks to diabetes and hypertension, among other small vessel diseases, is well known; its application to sickle-cell disease is clearly demonstrated in this study. In the five cases of sickle-cell disease reported, kidney dysfunction of varying degree was found in association with the retinal vascular pathology, and in three cases abnormalities of the conjunctival vessels also appeared to be present. This serves as additional evidence that in retinopathies with vascular involvement as the primary lesion the study of conjunctival vessels and kidney function can be of value in determining whether the pathology is local or part of a generalized vascular disease. Conversely, where kidney pathology is found and a primary vascular disease is suspect, the retina and conjunctiva may be studied for visible evidence of small vessel pathology.

Summary

Ocular findings in five patients with sickle-cell disease are described. Hemoglobin electrophoresis demonstrated sickle-cell hemoglobin C disease in four cases and suggested sickle-cell hemoglobin D disease in another. Fundus changes included retinitis proliferans, aneurysmal vascular dilatations, arborizing vascular networks, focal constriction, dilatation, sheathing and obstruction of arterioles and venules, the development of chalk-white vessels owing to changes in intravascular contents, preretinal hemorrhages which closely simulated retinal tears, and vitreous and retinal hemorrhages. Vascular changes were also noted on the optic disk and bulbar conjunctiva. Histologic findings in one patient with sickle-cell retinopathy showed retinal and vitreous hemorrhage, retinal gliosis blending with a preretinal fibrous membrane, extensive new vessel formation, obliterated vessels, perivenous lymphocytic cuffing, and sickled cells intravascularly and in the areas of hemorrhage.

Hemoglobin genealogies are cited for three of the patients, including a family with sickle-cell hemoglobin C disease in the mother and a normal father. The results support the postulate that hemoglobins S and C are allelic or closely linked.

The findings in these patients are discussed in relation to previous reports of sickle-cell retinopathy, the pathophysiology of sickle-cell disease in other organs, and the correlation of ocular pathology with the different genotypic forms of sickle-cell disease. The following points are stressed:

1. Sickle-cell retinopathy may be manifest as an acute or chronic obstructive vascular disease, with vitreous hemorrhage as a frequent complication. The occurrence of such pathology in Negroes or in Caucasians of Mediterranean origin warrants testing for a sickling tendency and performance of hemoglobin electrophoretic studies if sickling is present. All cases of Eales' disease reported in these groups should be reinvestigated for evidence of sickle-cell disease.

2. The major features of sickle-cell retinopathy can be accounted for on the basis of vascular stasis and obstruction involving both arterial and venous systems. This is the common pathologic denominator of sickle-cell disease in the organs which it affects.

3. The small number of reported cases of sickle-cell retinopathy, as well as the inadequacies in either the ophthalmologic or the hematologic examination of these patients, makes it impossible to reach any conclusion regarding the incidence of retinopathy in the different types of sickle-cell disease. However, it is noted that patients with sickle-cell hemoglobin C disease appear especially prone to ocular manifestations.* Furthermore, sickle-cell trait may also lead to eye complications, as well as obstructive vascular episodes in other organs, and should no longer be considered a clinically benign carrier state.

4. Renal and ocular pathology are frequently associated in sickle-cell disease, as in other "small vessel" diseases such as hypertension and diabetes.

Dr. Harvey A. Itano (National Institute of Arthritis and Metabolic Diseases) gave guidance in the hematologic and genetic phases of this investigation. Miss Elizabeth Robinson performed the hemoglobin electrophoretic studies; Dr. Hans Keitel performed special kidney-function tests; Mr. John Parker made the fundus drawings, and Mr. Fred H. Meiller did the photomicrography.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (14).

* Since completion of this paper two new cases of sickle-cell hemoglobin C disease and retinitis proliferans have been brought to our attention.[55,56] In addition, in a recent paper by Kennedy and Cope[57] another similar observation is described. They also make reference to patients with sickle-cell trait and sickle-cell anemia who showed fundus lesions probably associated with the hemoglobinopathy. Not included in this paper are two young Negro patients with sickle-cell anemia observed in this Institute, who showed ophthalmoscopically the characteristic fundus changes of angoid streaks. They will be described in a later report.

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Increased Intracranial Pressure Without Papilledema

PAUL LEVATIN, M.D., Oakland, Calif.

A tumor exerting pressure on an optic nerve eventually causes optic atrophy. As it enlarges and finally causes elevation of intracranial pressure, papilledema occurs in the opposite eye, but not in the eye with the optic atrophy, for in this eye the sheath about the nerve is closed by the tumor at the optic foramen so that the cerebrospinal fluid pressure cannot be transmitted to the nerve head. The syndrome of ipsilateral optic atrophy and contralateral papilledema due to a basofrontal or subfrontal tumor is called Kennedy's syndrome or, perhaps more correctly, the Paton-Kennedy syndrome. The most comprehensive paper on the subject since the original one by Kennedy in 1911 is that of Jefferson (1945),[1] who found 14 cases among 100 frontal lobe tumors and listed five variants of the syndrome.

In this paper are described a typical case of the Kennedy syndrome and also a variant not mentioned by Jefferson, consisting of bilateral optic atrophy without papilledema—in effect, a bilateral Kennedy syndrome.

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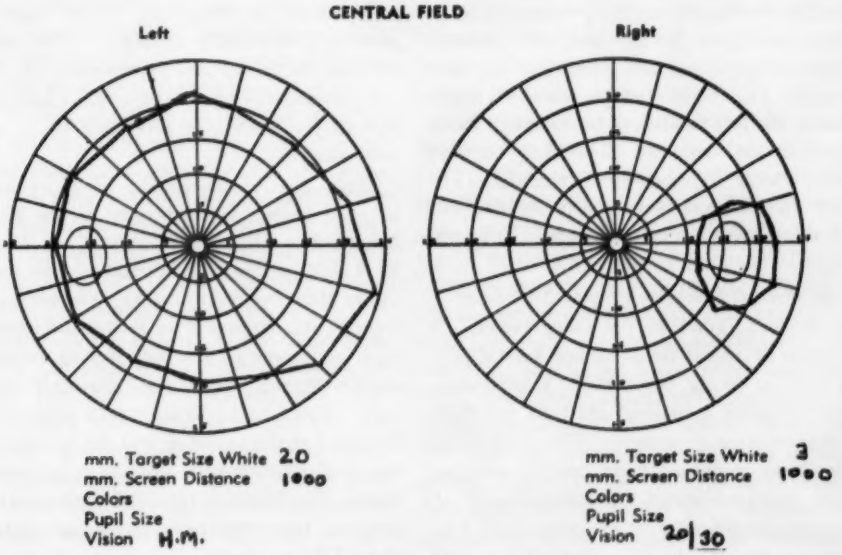
From the Department of Ophthalmology, Kaiser Foundation Hospital.

Report of Cases

CASE 1.—A 43-year-old housewife was referred in March, 1953, because of the finding that her left eye, which two years ago had had 20/20 vision, was now almost blind. Ophthalmological examination revealed that the vision of the right eye was 20/30 and that that of the left was reduced to the perception of hand movements. The pupils were equal, but the left reacted to light through a narrow arc only. There was papilledema of



Kennedy's syndrome, with an absolute central scotoma of 20 degrees in the left eye due to direct pressure of the tumor and an enlarged blind spot in the right eye due to papilledema.

2 D. in the right eye; the left disc was flat with temporal pallor. The peripheral visual fields were normal. The blind spot was three times larger than normal in the right eye. An absolute central scotoma occupied almost the entire central field of the left eye (Figure). A diagnosis of Kennedy's syndrome was made, and the patient was hospitalized.

The past history at that time revealed that three years previously the patient had had a "nervous breakdown" characterized by weakness, trembling, and flashes of light. For some months after this she was said to be constantly unstable and depressed; she had psychiatric care, and once she attempted suicide. Her depression gradually disappeared, and she had been asymptomatic until the occurrence of anosmia one year previously. Frontal headache had occurred eight months previously, with increased sensitivity to noise and disturbance of vision in the left eye. Three months later her headaches ceased. She complained now of difficulty in maintaining her balance, with a tendency to fall to the right. Recently she had noted some difficulty in concentrating, urinary urgency, and weight gain of 6 lb. in the previous month. Neurological examination revealed a slightly obese, pleasant woman with pathological jocosity and with inability to answer questions which required any deep thought. The right fundus showed papilledema; the left fundus, optic atrophy. There was bilateral anosmia. The deep tendon reflexes were hyperactive throughout. The abdominal reflexes were absent on the left, and there was a positive right Hoffmann sign.

On pneumoencephalography the ventricular system failed to fill from below. A specimen of spinal fluid showed a total protein level of 66 mg. per 100 cc. Ventriculography revealed a marked shift to the right of the ventricular system. The skull films showed no increased bone density such as occurs characteristically in meningiomas of the sphenoid ridge or olfactory groove. The diagnosis was made of tumor of the left frontal area, probably meningioma of the olfactory groove, and a craniotomy was done by Dr. Nathan C. Norcross.

At operation there was found a large left parasagittal meningothelial meningioma, weighing 97 gm. It arose from the anterior part of the sagittal sinus, pushing the frontal lobe backward and growing along its inferior surface. It had displaced the falx cerebri considerably to the right, compressing both olfactory bulbs and the sheath of the left optic nerve. As a result of large vessels growing into the tumor bleeding was profuse, and it was necessary to amputate the frontal lobe in part, but the tumor was removed in toto. Recovery was rapid. She was last reexamined in September, 1956, three and one-half years after operation. Her husband stated that her memory was almost perfect and that she was able to carry on the full activities of a housewife. There was a residual slight right hemiparesis, and the vision of the left eye remained reduced to finger counting. The right fundus was normal. The left disc was very pale, with no capillaries on its surface. There was no sheathing of the vessels; the arteries were not narrowed, and the edges of the disc were distinct. The visual fields were unchanged except that the blind spot in the right eye was only minimally enlarged. The central scotoma in the left eye persisted.

Comment.—This is a clear-cut example of Kennedy's syndrome produced by a large meningioma.

CASE 2.—A 12-year-old boy, previously in good health, was admitted to the Kaiser Foundation Hospital, Oakland, in March, 1954, complaining of headaches and vomiting of three weeks' duration. The headaches were at first frontal, later severe and generalized, and some of the episodes of vomiting were without prior nausea (projectile vomiting). There was a history of a blow to the forehead at the age of 4, and the left eye had deviated outward with amblyopia for several years. Examination revealed a muscular intelligent boy; the only abnormal findings were left exotropia, pale optic discs, and absent right knee jerk.

Lumbar puncture on admission showed clear colorless fluid under 430 mm. pressure with 110 erythrocytes per cubic millimeter (25% crenated) and a 1+ Pandy test. The total protein was 93.0 mg. per 100 cc.; the quantitative Kolmer test was negative, and the Lange colloidal gold curve was 445332100. Skull x-rays showed no abnormality, and x-rays of the wrists and knees showed no lead lines. The blood cell count, urine studies, and Kahn and heterophile agglutination tests were negative. The neurologist suspected a subarachnoid hemorrhage from a leaky aneurysm or a parasellar tumor. The neurosurgeon recommended ventriculography to rule out an intracranial mass.

Ophthalmological consultation revealed that the right pupil measured 5.0 mm. and the left pupil, 5.5 mm. They reacted well to light. The optic discs were flat and moderately pale, with clear edges. There were three capillaries on the right disc and four on the left disc. The retinal vessels were normal. There was a left exotropia of 60△ for distance and 30△ for near. A manifest refraction showed R. E., $-1.00-1.00\times180$ degrees $=20/30+$; L. E., $+1.00-2.25\times10$ degrees $=20/400$. By confrontation test, the visual fields were full. With a 3/330 white test object, the peripheral field of the left eye was normal and that of the right eye showed a slight temporal contraction, of approximately 10 degrees. Central fields with a 1/330 white test object on the Ferree-Rand perimeter showed the right blind spot to be enlarged 4 times and the left blind spot, approximately 10 times. Diagnoses made were (1) optic atrophy, partial, primary, bilateral; (2) left exotropia with amblyopia ex anopsia, left eye.

Because of the absence of papilledema in spite of the high spinal fluid pressure, the lumbar puncture was repeated five days later. Again the initial pressure was 430 mm., with 250 erythrocytes per cubic millimeter (mostly crenated cells) and a total protein value of 126 mg. per 100 cc., with a colloidal gold curve of 445433210.

Two weeks later, ventriculography was performed. The cerebrospinal fluid was under markedly increased pressure and squirted from the burr hole about 6 or 8 in. when a lateral ventricle was tapped. The ventriculograms showed a symmetrical dilatation of both lateral ventricles. The third and fourth ventricles were not visualized. That afternoon a right transfrontal craniotomy was carried out by Dr. Nathan C. Norcross, and the frontal lobe was elevated to expose the region of the chiasm. The right optic nerve was found to be almost completely surrounded by neoplastic tissue, from which it could not be separated. The main mass of the tumor, which was soft and contained many hemorrhages, presented medial to the right optic nerve. The left optic nerve was so surrounded by the tumor that it was never visualized. A transcortical incision was made to expose the anterior horn of the right lateral ventricle. Protruding through the foramen of Monro from the third ventricle into the right lateral ventricle was a cystic portion of the tumor. Further exploration of the third ventricle revealed that the tumor continued as a rather soft mass into the substance of the hypothalamus and into the anterior part of the lateral wall of the third ventricle. Biopsy specimens were taken. The tumor was considered inoperable. The patient died four days after surgery. Permission for postmortem examination was not obtained.

The microscopic description of the tissue specimens was given by Dr. Melvin Friedman. "The fragments of tumor from the region between the optic nerves have essentially the same pattern as those from the region of the thalamus, although the former have the greater number of small cysts. It is composed predominantly of astrocytes and unipolar and bipolar spongioblasts with relatively few other glial cells. Numerous small sized cystic spaces are formed by the tumor, and some of these contain blood, but they are not of vascular origin as demonstrated by reticulum and collagen stains. Although the relatively large number of spongioblasts would suggest the possibility of a spongioblastoma polare, the cystic pattern and the lack of fasciculation and the

absence of giant cells all point toward astrocytoma."

Comment.—It is impossible to say whether this glioma arose from the optic nerves or from the brain tissue surrounding the third ventricle above the chiasm. Primary gliomas of the chiasm occur most frequently at 12 to 14 years, and the histology of the biopsy specimens is consistent with the diagnosis of a primary glioma of the optic nerve. The marked amblyopia in the left eye was due to the more extensive involvement of the left optic nerve by tumor tissue, and the left exotropia was no doubt secondary to the amblyopia. The patient had on both sides what Foster Kennedy had described for one side. He had a tumor which, enveloping both optic nerves, had caused bilateral optic atrophy and had mechanically acted as a deterrant to the formation of papilledema in either eye.

General Comment

Foster Kennedy,[2] in his original paper (Case 6), described a patient who suddenly lost almost all the vision of both eyes as the result of an enormous glioma of the left frontal lobe which compressed both optic nerves. "In this last case, the tumor, by pressing on the optic nerves and olfactory bulbs of both sides produced bilaterally a symptom complex seen in the other cases on one side only." However, this case was listed by Kennedy among the three which had bilateral papilledema first, followed later by bilateral retrobulbar neuritis. Cushing and Walker[3] (1915) similarly explained the absence of papilledema in pituitary tumors with increased intracranial pressure, stating, "This we have attributed to the fact that the sheath of Schwalbe is so blocked as to prevent the crowding down of cerebrospinal fluid around the nerve—in other words, to an interference with the physical conditions under which a choked disc is produced." Chamlin, Davidoff, and Feiring,[4] (1955) in a series of 138 cases of pituitary tumor, found only 1 in which papilledema occurred as an early sign "and this was an unusual case in many respects." The authors did not record the frequency with which papilledema occurred in the late stages of the disease, when presumably increased intracranial pressure was present, but noted that in their three cases of carcinoma of the pituitary gland papilledema was not seen even at a very advanced stage of the disease.

It would seem that a glioma arising from the optic nerves at or near the chiasm would occlude the sheaths of the nerves at the optic canals before it could produce increased intracranial pressure by extension to the third ventricle. One of the diagnostic x-ray signs of an optic nerve glioma is an enlarged optic foramen. It is hard to imagine that a tumor which caused enough pressure to absorb the bony wall of the optic canal would not at the same time occlude the optic nerve sheath within the canal. If this view is correct, papilledema should rarely, if ever, be found in primary tumors of the chiasm.

Discussing chiasmal gliomas, Duke-Elder states, "Papilledema is a rare phenomenon and only occurs exceptionally unless the tumor has reached a size such as will cause a rise in intracranial pressure (Dandy 1922, Aitchison 1936)." However, Aitchison's[6] case of glioma of the chiasm was a patient with unilateral papilledema and no increased intracranial pressure. Dandy's[7] two cases were dural endotheliomas involving the optic nerves, with bilateral primary optic atrophy but no increased intracranial pressure. Martin and Cushing (1923)[8] among their seven cases of chiasmal glioma had only one with increased intracranial pressure demonstrable at operation. This 8-year-old boy showed "a bilateral primary optic nerve atrophy with a low grade of what was taken to be a superimposed papilledema on the right." Taveras et al.[9] (1956) reported 34 cases of gliomas of the optic nerve and chiasm. Papilledema was present in three of these, but it must be noted that these three were among the nine unverified cases in the group. Papilledema was present in none of the 25 cases verified by operation. Evi-

dently papilledema is rare in verified cases of chiasmal glioma.

Among their cases, Martin and Cushing had one (Case 5) with bilateral papilledema without increased intracranial pressure. At autopsy the elevation of the discs was shown to be due to gliomatous invasion of the optic nerve heads and entire optic nerves within the orbits. As a clue in making the difficult diagnosis of chiasmal glioma they stated, "Suspicion should be aroused when there is an obvious swelling of an atrophic nerve head without evidence of increased intracranial pressure." We should like to stress the opposite; namely, that suspicion of a glioma involving the chiasm should be aroused when there is an obvious increase of intracranial pressure but no papilledema, especially if primary optic atrophy exists. Thus, at a recent clinicopathological conference at the Massachusetts General Hospital (1956) [10] there was presented a patient who had normal fundi although repeated taps had shown a high spinal fluid pressure (520 mm.). Autopsy revealed a glioblastoma multiforme occupying the right cavernous sinus and the pituitary fossa. The tuber cinereum, the dorsum sellae, the chiasm, and the right optic nerve were lost in the tumor mass. The absence of papilledema was explained on the basis that papilledema could not develop within the short time (four days) of the patient's hospital stay. The length of time for papilledema to become discernible in a patient with such an elevated intracranial pressure is not known, but it would appear to have been impossible on the basis of these autopsy findings for papilledema to have ever developed in this patient.

Summary

If direct pressure of an expanding lesion on an optic nerve can mechanically prevent papilledema in that eye by occluding the subarachnoid space about the nerve (as in the Kennedy syndrome), then direct pressure on both optic nerves could reasonably be expected to prevent papilledema in both eyes. An instance of each of these phenomena is described. In one a large parasagittal meningioma produced ipsilateral optic atrophy and contralateral papilledema. In the other a glioma surrounding the chiasm and strangling both optic nerves produced bilateral primary optic atrophy with no papilledema in spite of increased intracranial pressure.

Conclusions

Increased intracranial pressure without papilledema in a patient with bilateral optic atrophy may be due to bilateral occlusion of the optic nerve sheaths. Such a syndrome may be caused by an expanding chiasmal lesion which extends along the optic nerves and occludes the optic canals, subsequently invading the third ventricle above it. This offers an explanation for the rarity of papilledema in verified cases of primary glioma of the optic nerves involving the chiasm. Thus, the finding of papilledema should help to exclude the diagnosis of glioma of the chiasm, just as it helps to exclude the diagnosis of pituitary adenoma.

Kaiser Foundation Hospitals, Permanente Medical Center, 280 W. MacArthur Blvd. (11).

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The Histology of the Glioma of the Optic Nerve

A Study with Silver Carbonate

LEOPOLD LISS, M.D., and J. REIMER WOLTER, M.D., Ann Arbor, Mich.

Primary tumors of the optic nerve are common, and more than 400 cases have been previously reported, but the histopathologic nature of these neoplasms is still in doubt.

The first to recognize the glial nature of the tumors of the optic nerve was Hudson,[1] who, in 1912, evaluated 182 cases, of which 118 were classified as "gliomatosis," and described four types of cells: (1) bipolar cells with oval nuclei and straight or spiral processes; (2) cells with thick, spiral processes; (3) stellate cells with branched processes, and (4) cells with round or oval nuclei and a variable amount of coarsely granular cytoplasm of circular or angular outline.

Verhoeff,[2] in 1921, classified tumors of the optic nerve as gliomas. He stated that this type of glioma is the only tumor arising primarily intraneurally (in contrast to mesodermal tumors arising in the dural sheaths). He also described various cellular forms composing such tumors, but he found spindle cells to be the most frequent type.

In 1943 del Rio Hortega[3] published his remarkable studies of the tumors of the optic nerve and distinguished several types of gliomas: (1) neoplasm formed by long cells (glioma longicellulare), (2) oligodendroglioma of the optic nerve, and (3) astroblastoma. He stated that the histogenetic origin and the nature of these neoplasms are frequently in doubt.

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From the Laboratory of Neuropathology and Neuroophthalmology, Neuropsychiatric Institute, University of Michigan Hospital.

For the present investigation an optic glioma with typical clinical features was used. Numerous variants of the silver carbonate technique (Scharenberg and Zeman,[4] Scharenberg,[5] Liss[6]) have been employed to analyze the histological structure of this glioma.

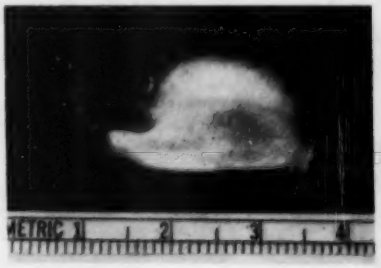
Clinical Course

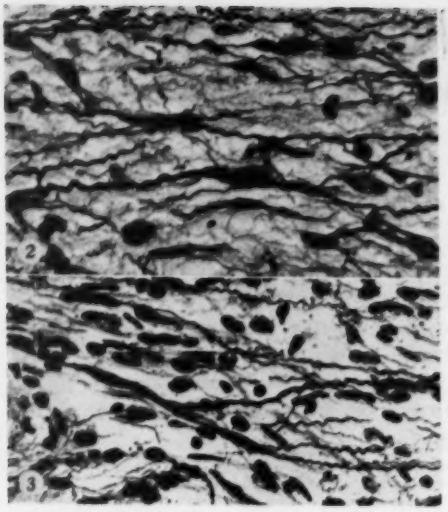
A 4½-year-old girl was admitted to the University Hospital with a two-month history of proptosis and decreasing vision in the left eye. An osteoplastic craniotomy was performed, and a tumor of the left optic nerve was removed. Two years after the operation there were no clinical signs of recurrence.

Pathological Examination

The spindle-shaped tumor measured 2.5×2×1.5 cm. and was covered by intact dura. On longitudinal section could be recognized (1) optic nerve, which was infiltrated by tumor and gray, with small hemorrhages and (2) extraneural tumor tissue, which had infiltrated the meninges and was white (Fig. 1).

Fig. 1.—Gross view of the tumor. The intra- and extraneural parts of the tumor can be grossly differentiated.

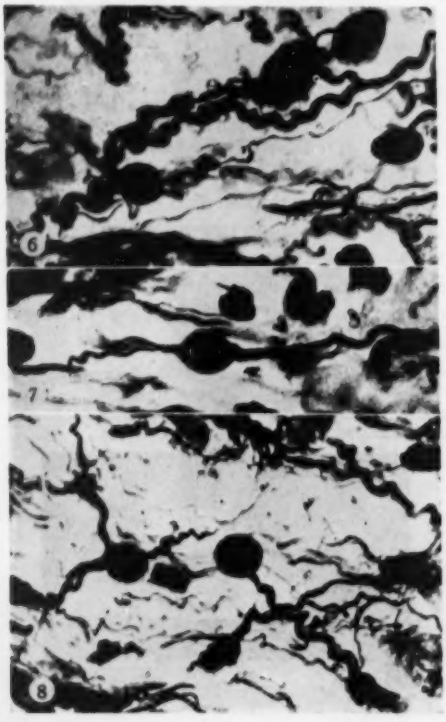




Figs. 2 and 3.—Elongated and spindle-shaped elements (Schwann cells). Photomicrograph. Zeiss Neofluar 40 ×.

Figs. 4 and 5.—Transitional elements between Type I (Robertson) and Type IV (Schwann) cells. Photomicrograph. Zeiss Neofluar 40 ×.

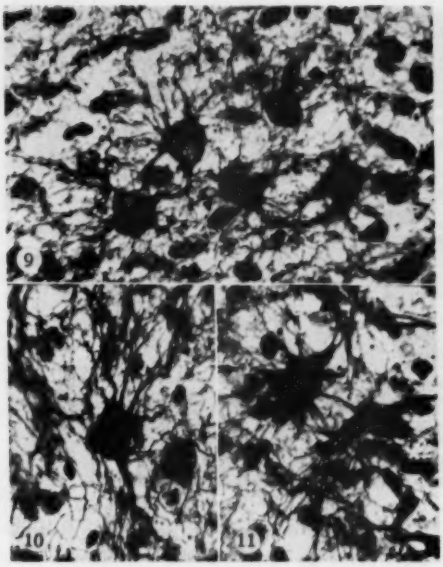
Figs. 6, 7, and 8.—Various forms of oligodendroglia. Photomicrograph. Zeiss Neofluar 40 ×.



The cellular elements in the intra- and extraneural part of the neoplasm revealed a great variety of forms. Very numerous were cells with an oval body and nucleus, sparse cytoplasm, and two or more very long well-developed processes of different caliber and shape, spiral or straight (Fig. 2). Cells of another variety were bipolar and slender, with elongated nuclei; their processes were exceptionally long and wavy and were frequently only slightly thinner than the body of the cell (Fig. 3). There were numerous transitional types; some had a round nucleus and numerous very long processes which were shaped like spirals; others had irregularly formed bodies and powerful, thick processes (Figs. 4 and 5).

There were numerous large elements with oval or spherical bodies and two or more powerful wavy processes. These elements resembled oligodendroblasts (Fig. 6) and oligodendrocytes (Figs. 7 and 8).

An entirely different type was represented by cells with polygonal bodies and numerous fine, short or long, radiating processes. Cells of this variety were present either in clusters (Fig. 9) or singly (Fig. 10), and their

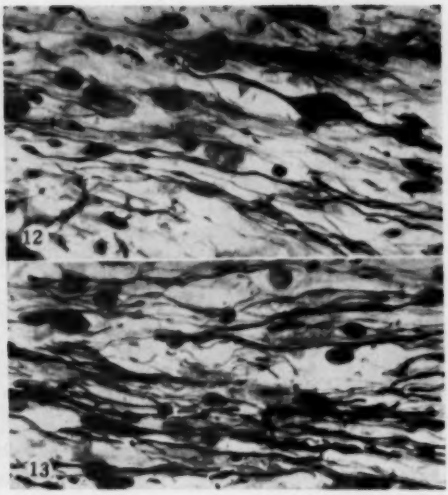


Figs. 9, 10, and 11.—Astrocytic elements. In cluster (Fig. 9); single cell (Fig. 10); cell with processes attached to blood vessel (Fig. 11).

processes occasionally connected with vessels (Fig. 11). These elements represent transitions between astroblasts and oligodendroblasts.

The invaded optic nerve still contained numerous nerve fibers (in bundles or singly), which showed signs of degeneration such as swellings, Cajal's bulbs, and advanced disintegration (Figs. 12 and 13).

The leptomeninges were greatly thickened; their connective tissue structures were



Figs. 12 and 13.—Optic nerve fibers from the tumor with swellings and Cajal's bulbs. Photomicrograph. Zeiss Neofluar 40 ×.

proliferated and formed a dense interwoven network which was invaded by countless neoplasmatic cells (Fig. 14). These cells were histologically identical with those in the optic nerve, but the pattern of the tumor differed from that of the intraneural neoplasm and was determined by that of the proliferated connective tissue (Fig. 15). The difference in pattern of the extra- and intraneural parts of the tumor is shown in Figure 15, which represents the borderline between both varieties. The upper part of the photomicrograph (infiltrated meninges) shows the tumor cells which fill the meshes

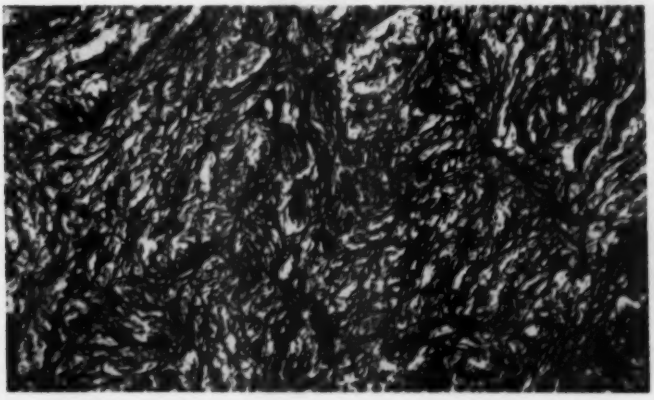


Fig. 14.—Connective tissue pattern in the extraneural part of the tumor. Photomicrograph. Zeiss Neofluar 6.3 ×.

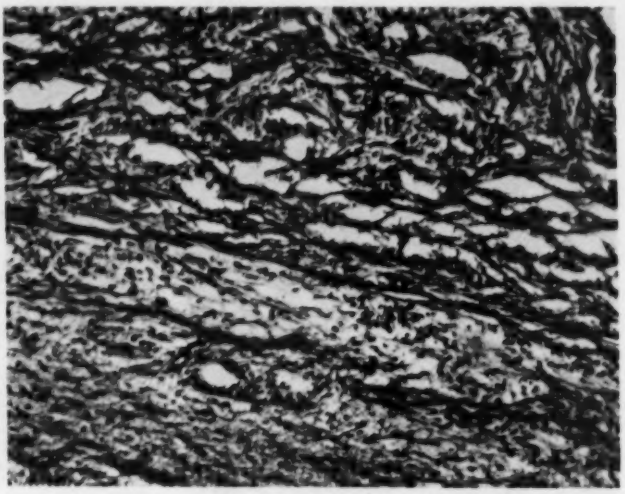


Fig. 15.—Borderline between the intra- and extraneural part of the tumor (connective tissue impregnation). Photomicrograph. Zeiss Neofluar 6.3 ×.

of the connective tissue. The pial sheaths which separated the two parts of the tumor are intact in the area photographed; in other parts they were frequently interrupted by masses of tumor cells. The lower part of Figure 15 (intraneural part of the tumor) shows the parallel arrangement of the blastomatous cells. Figure 16 shows the relationship between the tumor cells and the blood vessels; all types of the cells form an elaborate perivascular structure. The connective tissue sheaths, which in this part of the tumor have the usual arrangement of their fibers, determine also the parallel course of the majority of the blastomatous elements (Fig. 17).

Comment

The cellular elements which form the tumor can be classified into three types. The first variety are the elongated, or spindle-formed, mostly bipolar, Schwann elements. The second variety is the round multipolar oligodendroglia. There is no sharp division between these two types, since there are many intermediate forms. To the third type belong the astrocytes, respectively, astro-

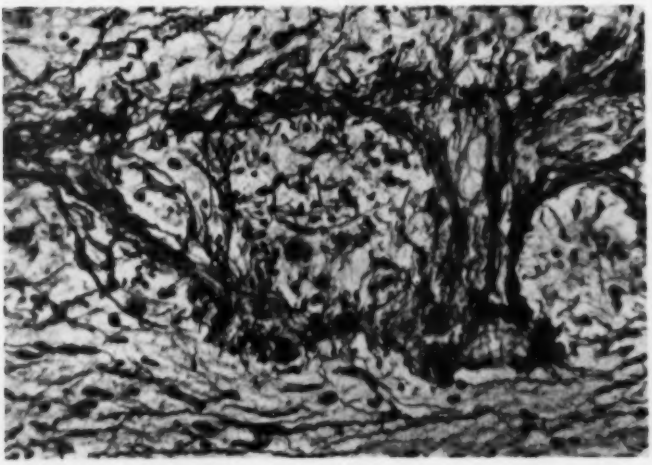


Fig. 16.—Perivascular structures formed by tumor cells in the intraneural part of the tumor. Photomicrograph. Zeiss Neofluar 16 ×.

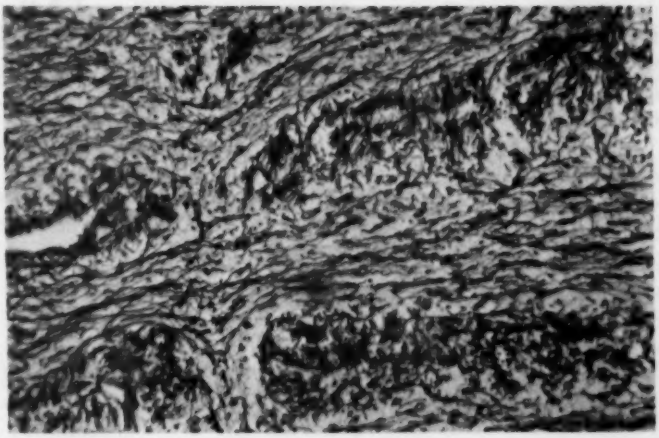


Fig. 17.—Parallel arrangement of the neoplastic elements in the intraneural part of the tumor. Photomicrograph. Zeiss Neofluar 6.3 ×.

blasts. The majority of authors believe that the "topographical relationship" (Christensen and Anderson [7]) of these tumors cause their specificity, but they are formed mostly by oligodendroglia, Schwannoid elements, or astroglia (Wilson and Farmer,[8] Bailey and Eisenhardt,[9] Bailey,[10] François and Rabacy [11]), although Martin and Cushing [12] believe that the tumors arising in the optic tract may be of various types, as is true for the gliomas elsewhere in the brain. Lundberg [13] reported nine tumors, which he classified as oligodendrogliomas, which have both the oligodendroglia and Schwannoid elements equally represented. The atypical forms of astroglia which were found in these tumors were interpreted by this author as intermediate forms between the astroglia and the oligodendroglia.

With the silver carbonate method, del Rio Hortega [3] distinguished three type of gliomas in the optic nerve: (1) neoplasms formed by long cells (glioma longicellular), (2) oligodendroglioma, and (3) astroblastoma. The last-mentioned is characterized by a perivascular arrangement of its elements; it will not be discussed here.

The elongated elements of the "glioma longicellular" are peculiar to Schwann cells seen in both the peripheral and central Schwannomas (del Rio Hortega); all of these cells are identical with oligoglia Type IV (Schwann), while elements with oval or round bodies correspond to the oligoglia of Type I (Robertson).

In the tumor here described, the most common are cells of Schwannoid type, which are identical with the long cells of Hortega; in addition, there are numerous forms which mimic oligodendroglia of Type I and others definitely identified as blastomatous oligodendroblasts. A third variety is less well differentiated—they are large elements similar to blastomatous astroblasts. We are dealing, therefore, with a complex tumor which contains oligodendrocytes of various types. The presence of astroblast-like cells represents no contradiction, since astrocytes and astroblasts occur in a high percentage of oligogliomas.

This case of optic glioma shows characteristic invasion of the subdural space (Verhoeff). The pattern of the tumor cells is not influenced by the lack of nerve fibers, which the Schwann cells normally support (Lundberg), but follows closely the framework of the well-developed connective tissue. In the intraneural part this pattern arises from the parallel blood vessels, and in the extraneural part, from the irregular meshes of the pia-arachnoid. In the classification of this tumor, only the oligodendroglia and the Schwann elements can be considered important. The astroglial and astroblastic elements are represented in small numbers, in the same way as in the oligo-

dendrogliomas of the hemispheres, where they also appear as transitional forms between the astro- and oligodendroglia (Scharenberg). Of the two described types of cells, neither can be described as predominant. The tumor should therefore be classified as oligodendroglioma, since the two types represent only different degrees of maturation, adaptation to different requirements. As shown by Scharenberg, the blastomatous oligodendroglia is capable of reproducing the normal activities of oligodendroglia, such as satellitosis around ganglion cells and spirocyte formations around the neurites, or it may even appear to be like the Schwann elements. In the optic nerve, which is composed of nerve fibers but not of ganglion cells, the oligodendroglioma produces vast amounts of Schwann elements in different stages of maturation.

Summary

An optic nerve oligodendroglioma from a 4½-year-old girl was studied with variants of the silver carbonate technique. Various types of blastomatous oligodendroglial elements which formed the tumor are described.

Neuropsychiatric Institute, University of Michigan Hospital.

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Fungus Keratitis (Aspergillus Fumigatus)

Treatment with Nystatin (Mycostatin)

ANITA B. MANGIARACINE, A.B., and SUMNER D. LIEBMAN, M.D., Boston

Our purpose in this communication is to report the first case of Aspergillus keratitis treated with nystatin (Mycostatin). It is also our purpose to emphasize the importance of making an etiologic diagnosis before instituting treatment in severe corneal infection.

Ley and Sanders [1] recently reported three cases of severe hypopyon keratitis in all of which unidentified fungi were demonstrated on pathologic examination. The authors point out that since the introduction of antibiotics and corticosteroids the incidence of reported cases of fungus keratitis has been rising rapidly. They also stress the importance of suspecting fungus infection in cases of hypopyon keratitis and of carrying out adequate etiologic investigation. In a study of experimental fungus infection of the cornea, Ley [2] showed that oxytetracycline potentiated Candida albicans infection of the immature rabbit cornea. He also showed that there was an 80% average incidence of experimental fungus keratitis in cortisone-treated eyes as contrasted with a 20% average incidence in the controls. The cortisone was administered subconjunctivally.

Mitsui and Hanabusa [3] reported four cases of mycotic corneal ulcers, all of which followed topical cortisone therapy. In two of their cases Aspergillus fumigatus was identified. Cauterization, applications, of methylrosaniline chloride (gentian violet), sodium propionate, and trichomycin ointment seemed to have little beneficial effect, although the ulcers eventually healed and the inflammation slowly subsided after several weeks, leaving dense leukomas.

Tanaka [4] claimed that the incidence of Candida in the conjunctiva was not increased by antibiotic treatment. She stated that, in vitro, tetracycline actually inhibits growth of Candida. Her results are in contrast to those of Ley,[2] Seligman, and Dukes and Tettenbaum,[10] all of whom found that chlortetracycline, oxytetracycline, and tetracycline (broad-spectrum antibiotics) markedly potentiated experimental Candida infections. Penicillin, streptomycin, chloramphenicol, bacitracin, and sulfacetamide, however, did not show this potentiating effect.

Up to the present time, there have been no specific fungicidal agents available, although iodides have been used empirically to combat fungus infections. Schardt [5] cultured Nocardia organisms from a corneal ulcer and successfully treated the patient with tetracycline. Hervouet and Lenoir [6] recently described two cases of aspergillosis corneae. The first was diagnosed by smears and scrapings and was treated with strong iodine (Lugol's) solution U. S. P. intravenously and local application of tincture of iodine. The ulcer perforated, and the patient developed peripheral anterior synechiae, secondary glaucoma, and cataract. The second case was discovered during microscopic examination of a corneal button excised for transplantation. In this case, the organism could not be positively identified as an Aspergillus. The authors state that patients with A. fumigatus infections are always debilitated and usually have been working with agricultural products. They noted the frequent presence of a pseudo-

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From Departments of Ophthalmology, Massachusetts Eye and Ear Infirmary and Harvard Medical School.

membrane. Belicard[7] was the first to use nystatin in fungus keratitis. The organism in his case, however, was Streptomyces berardinisi. The diseases responded favorably to systemic administration of the drug.

Nystatin is an antifungal antibiotic derived from cultures of Streptomyces noursei and has been primarily used to combat moniliasis. The oral medication has been used for intestinal C. albicans infection, and the ointment, for the dermatomycoses, perlèche, paronychia, and similar conditions. In vitro studies[8] suggest that this type of antifungal agent inhibits or kills all species of fungi except Actinomycetes. It is claimed by Sternberg et al.[9] to be relatively nontoxic and to have produced no cases of sensitivity thus far.

Report of a Case

History.—A 37-year-old white male laborer was admitted to the Massachusetts Eye and Ear Infirmary on June 29, 1956, complaining of pain, photophobia, and blurring of vision in the left eye of 10 days' duration. He stated that while he was baling hay some of it had blown into his left eye. The ensuing redness and irritation was treated with some unidentified drops by a local first-aid man. Two or three days after the initial injury, a wad of grass discharged by a power lawnmover is said to have struck the left eye, aggravating the initial injury. About four days prior to admission he was seen by a physician, who prescribed some eye drops. Three days later the vision became much more blurred and the redness and pain were extreme. He was then referred to the Massachusetts Eye and Ear Infirmary.

Fig. 1.—Patient's eye on admission.

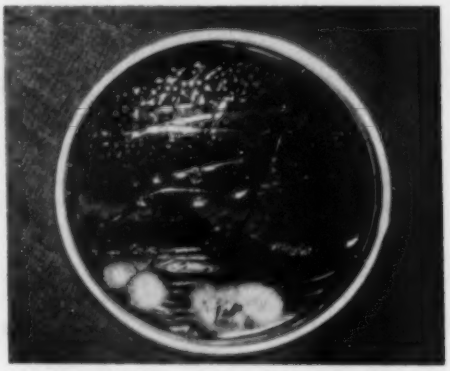

Fig. 2.—Colonies of the fungus as grown directly on blood agar from the corneal lesion.

On admission, the right eye was normal and its visual acuity was 20/30. The left eye showed edema of the upper lid, severe ciliary injection, a large grayish-white central corneal ulcer measuring about 5 mm. in diameter, and a 3 mm. hypopyon. No red reflex nor any fundus details could be seen with the ophthalmoscope. The pupil was small and reactive. Visual acuity in the left eye was reduced to counting fingers at 1 ft. There was a pterygium extending 2.5 mm. onto the cornea from the nasal side. Very little discharge was noted in the conjunctival sac, and no pseudomembrane was seen. The photograph in Figure 1 was taken on admission. Scrapings of the ulcer were stained with Gram's stain, methylene blue, and Giemsa stain and immediately examined. These all showed the presence of many neutrophils, spores, and mycelia but no bacterial forms. Bacterial and fungus cultures were taken and planted in duplicate on blood agar, Sabouraud's agar, and meat infusion broth. One set was left at room temperature, and the other set was incubated. After a few days the presence of fungi was noted on all media. The species was later identified as A. fumigatus by hanging-drop cultures. Figure 2 shows a photograph of the

Fig. 3.—Direct smear of the corneal lesion showing the fungus.

initial growth as cultured directly from the ulcer, and Figure 3 shows a photomicrograph of the direct smear.

Because it was thought that antibacterial antibiotics might encourage the growth of the fungus (demonstrated in the original scrapings), these medications were not used. Instead, oral nystatin therapy was instituted, and 500,000 units were administered every eight hours. A suspension of nystatin † was instilled into the conjunctival sac every two hours, beginning on the second hospital day. In addition, the patient was treated locally with atropine sulfate 4% solution, zinc sulfate 0.5% solution, frequent warm saline irrigations, and hot compresses. On the first, second, third, fifth, and seventh hospital days, the ulcer was "pasteurized" with a strabismus hook heated to a cherry-red color and held 1 to 2 mm. above the ulcer. Slight desiccation of the surface of the ulcer was observed during these treatments. On the third and fifth hospital days methylrosaniline chloride 1% was applied to the ulcer. During the course of the first week a creamy white infiltration appeared along the upper border of the ulcer. On the fifth hospital day saturated solution of potassium iodide was administered orally three times a day after meals. This was discontinued on the 21st hospital day, when the patient complained of nausea. After one week of this regimen the hypopyon gradually subsided, although the eye continued to be inflamed and painful. Meperidine (Demerol) and salicylates were barely adequate to control the pain. On the sixth hospital day smears and cultures of the corneal scrapings were negative for fungi and bacteria.‡ Nevertheless, the eye continued to be very inflamed and painful. Therefore, the nystatin drops were discontinued two days later, since it was thought that they might possibly be irritating to the eye. However, during the next four days, there was no further improvement. Figure 4 is a photograph showing the eye on the 12th hospital day. The hypopyon

† This suspension was prepared by Dr. John Murphy, Chief Pharmacist, Massachusetts Eye and Ear Infirmary, as follows. The pure lyophilized sterile nystatin powder (500,000 units) was ground up and suspended in 10.00 cc. of the following vehicle: NaCl 1.2 gm., chlorobutanol 0.5 gm., H_2O q. s. to 100.00 cc.

‡ Repeated bacteriologic studies on the 9th and 18th hospital days were also negative. Complete blood cell count, blood smear, urine, and chest x-rays were within normal limits.

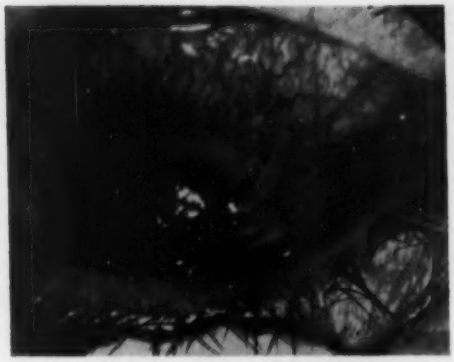

Fig. 4.—Patient's eye on the 12th hospital day.

had disappeared, but the eye was still considerably inflamed. Therefore, on the 14th hospital day, the patient was given typhoid vaccine by constant intravenous drip over a period of four hours. The febrile response reached a peak at 104.4 F and was maintained above 103 F for three hours. Slight improvement occurred during the next few days. On the 20th hospital day the patient complained of severe pain and the hypopyon reappeared. Resumption of orally administered nystatin was followed by strikingly rapid subsidence of redness and pain and by prompt regression of the hypopyon. Stromal edema in the region of the ulcer began to disappear, and, on the 32d hospital day, nystatin was again discontinued. The patient was discharged on the 35th hospital day with a central corneal scar in the eye, which was still slightly inflamed. His visual acuity was 20/200 with dilated pupil. On Aug. 10, 1956, one week after discharge, the left eye was almost white and quiet. There was a corneal scar. With a normal pupil, visual acuity was 10/200.

Comment

It is difficult to say to which measure the infection yielded; it could well have responded to a combination of therapeutic measures. However, the fact that the hypopyon recurred when the nystatin was stopped and rapidly subsided when the nystatin was readministered suggests that the drug played an important part in eliminating the fungus infection. This impression is reinforced by the rapid sterilization of the ulcer as demonstrated by repeated smears and cultures of the corneal scrapings. Obviously, more experience with this type of antifungal agent is needed before firm conclusions can be drawn.

Summary

Successful treatment of a case of hypopyon keratitis caused by Aspergillus fumigatus is reported. Nystatin, (Mycostatin), a specific antifungal agent, was used both locally and systemically and is believed to have exerted a beneficial effect. Immediate etiologic diagnosis averted the use of antibiotics known to aggravate fungus keratitis. This case emphasizes the established principle that corneal ulcers, especially those resulting from agricultural injuries, should have scrapings and cultures taken before treatment with antibiotics or corticosteroids.

Dr. Henry F. Allen made suggestions in the preparation of this report.

243 Charles St. (14).

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Differential Diagnostic Difficulties in Atypical Retinoblastoma

Report of a Case

SPRINZA WEIZENBLATT, M.D., Asheville, N. C.

The diagnosis of retinoblastoma is ordinarily not difficult; the symptoms vary with the stage at which the disease is detected. Its early stages have only been observed in the less-involved eye of bilateral cases, consisting of a whitish gray prominent focus, single or multiple in the posterior part of the retina. According to the larger statistics reported in the literature, the peak of incidence of this tumor is in children between 2 and 3 years of age. In Wintersteiner's [1] monograph, of 467 cases, less than 3% were 7 years old; in the series of Moorfields Hospital, Duke-Elder,[2] with 163 cases, had an even smaller percentage of this age, and Dollfuss and Auvert,[3] in a tabulation of 889 cases, noted only 1.6% for this age group.

As long as the disease is confined to the posterior segment of the eyeball the differential diagnosis is concerned with metastatic retinitis, Coats' disease, traumatic retinal detachment, retrolental fibroplasia, and some congenital malformations. At a later stage, when the tumor has involved the vitreous, the iris, and the anterior chamber, uveitis poses a differential diagnostic problem. Such cases have been mistaken for tuberculous iridocyclitis in the past.[2]

In a recent report by Manchot,[4] on 15 eyes removed in children with the clinical diagnosis of retinoblastoma, in only 50% was the diagnosis proved correct on pathologic examination. On the reverse side was the case of an 8-year-old child with the clinical diagnosis of tuberculous iritis whose blind eye was removed because of severe pain, in which the pathologic examination revealed a retinoblastoma with metastatic nodules on the iris.

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Report of Case

An 8-year-old white boy was first seen on Sept. 19, 1953, because of an inflammation and impaired vision in the left eye. He was an only child, very well-developed physically and mentally. His health had been good except for mastoiditis at the age of 3 years. Family history was negative for ocular diseases or blindness.

His present eye trouble began in May, 1953, about two to three weeks after a bout of measles. However, in retrospect, the parents remembered that he had complained of visual impairment in the left eye the year before. He reported to them that on the occasion of a visual screening at school in 1952 (about eight months previous to his manifest ocular trouble) he peeped with his right eye in order to see when the left was tested. As the eye appeared normal to the parents and as he denied having pain, this complaint was ignored. A few weeks before the onset of the inflammation, in May, 1953, the parents noted that the child squinted or closed the left eye when exposed to sunlight. The first ophthalmologist to examine the patient noted ciliary injection of the eyeball in the lower half, vitreous opacities, and a gray focus in the fundus above the macula. The vision was reduced to counting fingers. The right eye was entirely normal. The diagnosis was uveitis. Soon afterward the patient was seen by two other ophthalmologists, who confirmed this

diagnosis. He was treated locally with atropine drops and with cortisone internally. The inflammatory symptoms receded; the visual impairment remained unchanged; cortisone therapy was soon interrupted because of resulting generalized edema.

At the time of my first examination his main complaint was the visual impairment of the left eye. The right eye was entirely normal, vision 20/20. The left eyeball was of normal size and pale; sclera, normal. The cornea was clear and shiny, with a few minute opacities on the posterior surface below the center, of the appearance of old keratic precipitates. The anterior chamber was clear and of medium depth. The iris was hazel (as in the right eye), of normal appearance and structure; the pupil was round and 6 mm. (mydriatic) in diameter; ocular tension was normal digitally; the lens was clear; in the vitreous balled and strand-like opacities were present. Fundus: The optic disc was peculiarly gray and prominent and was only recognized by the situation of the central retinal vessels, which were of normal appearance. The retina adjoining the disc was gray, infiltrated, thickened, and opaque. Below the disc there was noted a stippling of the retina, but no white spots were present. The macula had the appearance of a honeycomb degeneration. It was difficult to visualize clearly the fundus periphery, but no masses or retinal detachment were present. Visual acuity was counting fingers at 3 ft. Diagnosis: neuroretinitis and endophthalmitis of left eye.

The etiologic examinations for tuberculosis, syphilis, brucella, and tularemia were negative. The stool examination was positive for Necator americanus (hookworm) and Ascaris lumbricoides. Sabin-Feldman dye test for Toxoplasma was positive in a titer of 1:1024. On treatment the intestinal parasites were eliminated.

About three months later the ciliary injection of the eyeball recurred; on the posterior surface of the nasal corneal quadrant a few peculiar ring-shaped granular opacities were noted; in the anterior chamber (slit-lamp examination) large whitish slow-moving opacities were present. The left iris had become tremulous, and its color, gray-blue, differed considerably from that of the right one. There were no vessels on the iris, no nodules, and no ectropium uveae. The formerly round pupil had become vertically oval, but it reacted well to light and in convergence. No abnormal reflex from the pupil was noted. The appearance of the fundus and visual acuity remained unchanged. The ocular tension was normal. The patient attended school regularly, did very well, and was very active. Treatment consisted of atropine, hot fomentations, and supportive treatment. No treatment for toxoplasmosis was instituted, which was assumed to be the etiology of the endophthalmitis.

During the next three months the iris became more blue; the ocular tension was never over 25 mm. Hg. (Schiøtz). In May, 1954, a few lenticular opacities were noted in the posterior cortex of the lens and the visual acuity was reduced to counting fingers at 1 ft.

The patient continued to attend school and did very well in his studies. Sometime in July, 1954, he developed anorexia and he was referred for evaluation of his general and ocular condition to a large medical center by his family physician. There all tests, neurologic, allergic, etc., were negative, except for a very high titer of the Sabin-Feldman dye test for Toxoplasma (1:4096). The ophthalmologic consultant found the right eye entirely normal, and he wrote in his report that there existed a complicated cataract in the left eye; the anterior chamber was clear, and ocular tension was normal, and he commented on the peculiar dirty gray opacities on the posterior surface of the cornea. A marked sensitivity to Staphylococcus toxin was noted at the medical center, and this considered as the etiologic factor of his ocular disease.

He was discharged from the hospital, but he was readmitted shortly because his anorexia had worsened. During his stay

in the pediatric department he experienced a severe attack of ocular pain with vomiting. The ophthalmologic consultant found the anterior chamber cloudy; the lens, intumescent, and secondary glaucoma was present. A cataract extraction was done, from which he recovered well, but after two weeks there was only a faint fundus reflex obtainable.

When I saw him again, in September, 1954, after an absence of three months, the child had greatly changed; he had become nervous and apprehensive and had lost 10 lb., but he was still active.

The right eye was entirely normal, and vision was 20/20. Left eye: Some ciliary injection was present. The surgical scar near the upper limbus was ectatic and cystoid. The peculiar opacities formerly noted on the posterior corneal surface were absent. A few floating opacities existed in the anterior chamber. The iris was blue, dull, in parts atrophic, in others thickened, with a peripheral coloboma above; no nodules or vessels were seen. The pupil was drawn upward, and on it some lens capsule was visible. Ocular tension was 20 mm. Hg (Schiøtz). The vitreous was cloudy; no fundus reflex was obtainable, and light projection was faulty. Enucleation was advised, but this was refused. His general health continued to deteriorate; x-ray of the skull was negative; no calcifications were present. Neurologic examination revealed hypoactive reflexes of limbs, no paresis, and no stiffness of neck; there were no masses in the abdomen, liver spleen were of normal size; laboratory tests were negative, and the dye test for Toxoplasma was 1:256. Ocular tension increased during the next two weeks to 37 mm. Hg.

Enucleation was done on Sept. 25, 1954. The eyeball measured 24×23×23 mm.; the sclera was smooth, without ectatic areas or nodules. The optic nerve was thickened; its cut surface was dirty-gray.

Because of the possibility of a Toxoplasma infection (three high titers of dye test) the eye was opened and fresh material from the nasal calotte was inoculated into mice by Dr. Leon Jacobs, of the National Institute of Health, Bethesda, Md.

The inspection of the interior of the enucleated eye revealed the vitreous to be slightly milky-bluish, particularly over the corona ciliaris. There was no tumor mass in the retina, which was everywhere attached, opaque, and gray. The optic nerve head was prominent and of the same color as the retina.

For three days following the enucleation the patient's general condition improved, but he relapsed again with nausea and vomiting. He left the hospital five days after surgery, and at the next check-up, three days later, the socket had healed. The right eye was entirely normal; vision, 20/20; fundus, normal. On Oct. 8, 1954, he was readmitted to the hospital in critical condition; two hours previously he had suffered a convulsion, and his left side was paralysed. There was a fast horizontal nystagmus of the right eye; the pupil was 5 mm. in diameter and fixed. On fundus examination a hyperemia of the optic disc and of the retinal vessel was noted; no other pathology existed. As the spinal tap revealed considerable pressure (450 mm.), the neurosurgical and pediatric consultants advised ventriculography. The ventriculogram revealed an obstructive internal hydrocephalus in the region of the lower aqueduct or fourth ventricle. Suboccipital craniotomy was done, during which the patient died.

Partial autopsy (brain) was obtained. The dura was not unusual; on its removal the leptomeninges were seen to be somewhat congested and had a whitish granular appearance, particularly on the base, the posterior parts, and the cerebellum, where the granules were larger. These changes extended to the surface of the hemispheres, but to a lesser degree. Convolutions and sulci were not unusual. The optic nerves appeared thickened and were removed as far into the orbital as possible.

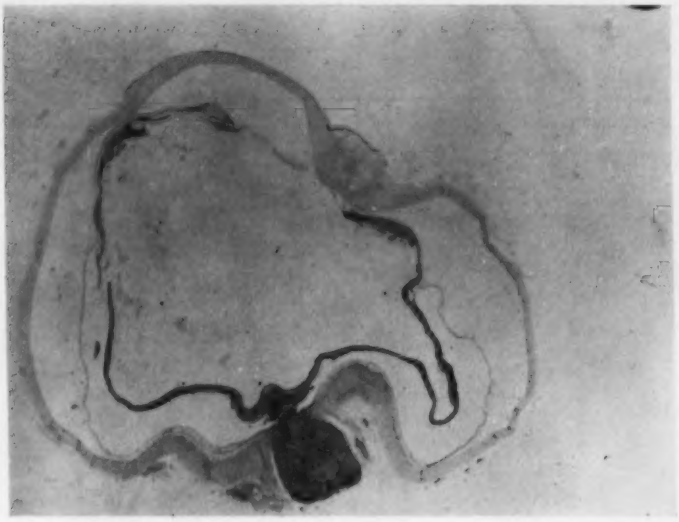


Fig. 1.—Photograph of eyeball, with cystoid scar at upper limbus. Neoplastic infiltration of entire retina and optic nerve; (A. F. I. P. Accession No. 677283, Picture No. 56-19953, × 4.)

Microscopic examination of eyeball. Bulbus partly collapsed (Fig. 1). The sclera and conjunctiva were normal. The subconjunctival tissue was thickened in the region of the surgical scar; it contained many new-formed capillaries and some hemorrhages as well as cystic spaces. On the posterior surface of this scar, adjacent to a cystic space, there was an accumulation of small round or polygonal cells of 6μ to 8μ in diameter with scanty cytoplasm and a relatively large oval dark-staining nucleus. The folded lens capsule, enclosing some lens matter, adhered to the posterior surface of the scar. The cornea was normal; on its posterior surface were present clumps and sheets of round cells with dark-staining nuclei of the same appearance as those adherent to the scar. These cells formed larger clusters near the angle of the anterior chamber and included pigment and nuclear fragments. Similar cells were noted

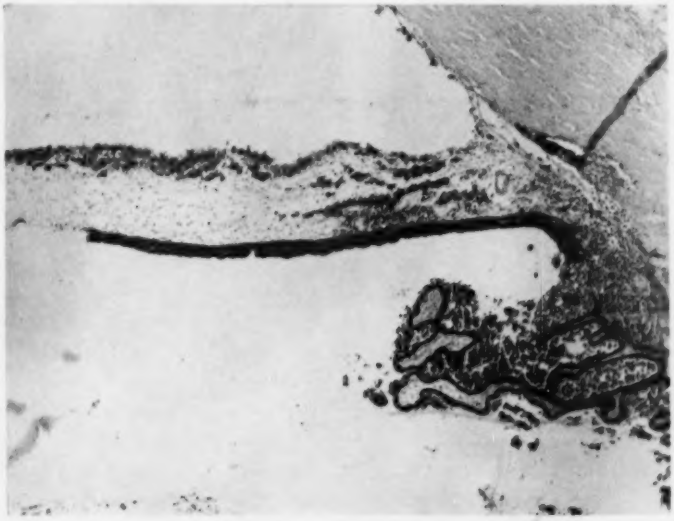


Fig. 2. — Photomicrograph of neoplastic growth on anterior surface and stroma of iris. Posterior pigment layers of iris partly destroyed by neoplasm. Metastatic growth around ciliary processes extending into ciliary body. Polymorphism of tumor cells. (A. F. I. P. Accession No. 677283, Picture No. 56-19960, × 50.)

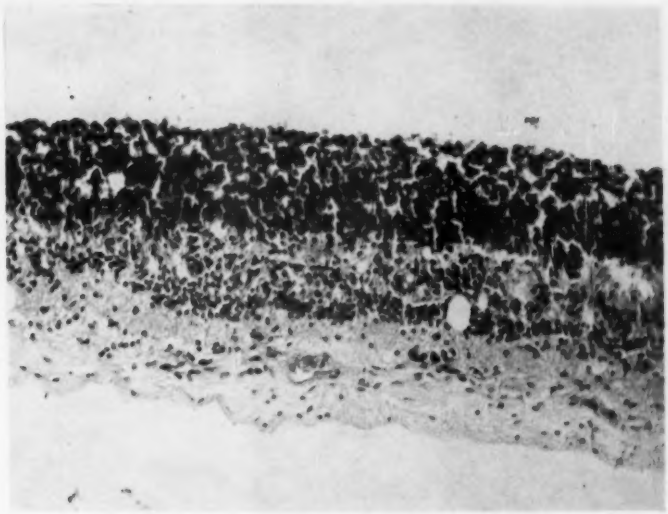
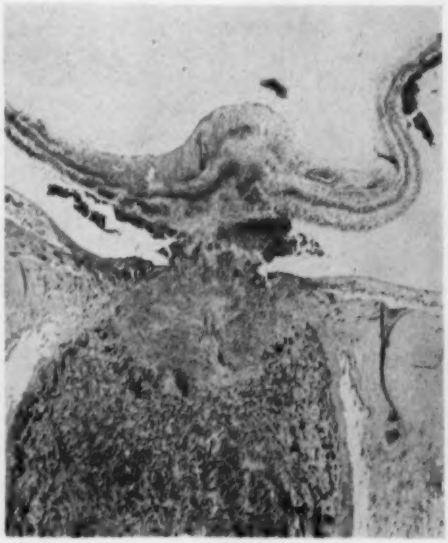


Fig. 3. — Photomicrograph of diffuse neoplastic infiltration of retina. (A. F. I. P. Accession No. 677283, Picture No. 56-19961, × 145.)

in the canal of Schlemm and between the trabeculae of the angle. In the anterior chamber a few red blood cells and clumps of neoplastic cells were present. The upper half of the iris was atrophic; a peripheral coloboma was visible in it. On its anterior surface neoplastic cells formed a turf; mitoses were present. In the iris stroma the tumor cells arranged themselves as a narrow band near the iris root. The posterior pigmented layers of the iris were absent over large areas and were partly replaced by tumor cells, which exhibited considerable variations in their size and shape. There was no ectropium uveae present; the iris muscles were intact. The lower half of the iris was similarly affected, except that its atrophy was less pronounced; there were no nodules on the iris surface. In the anterior part of the ciliary body below, a circumscript infiltration of tumor cells was noted; it was continuous with that which surrounded the ciliary processes (Fig. 2). The pars plana was covered by layers of tumor cells. The neoplastic cells around the ciliary processes and of the ciliary body were larger and more polymorphic than those of the anterior segment; their nuclei were vesicular with a nucleolus; mitoses were more numerous. The choroid was entirely free of tumor. The entire retina from the optic nerve to the ora serrata was infiltrated in the outer nuclear layer with closely packed tumor cells; the other layers were less affected. Cuffs of tumor cells were noted around the vessels of the

Fig. 4.—Photomicrograph of optic disc and nerve. Cuffs of tumor cells around large vessels in retina and nerve head. Avascular neoplastic growth between retina and pigment epithelium. (A. F. I. P. Accession No. 677283, Picture No. 56-23058, × 20.)



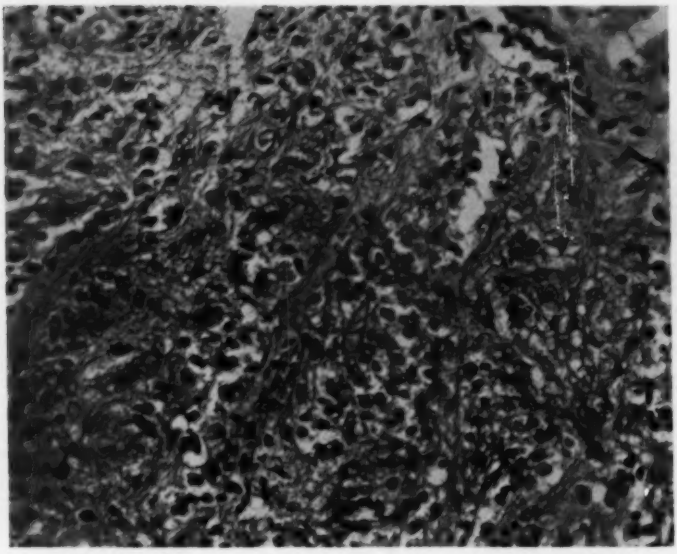


Fig. 5. — Photomicrograph showing polymorphism of neoplastic cells in optic disc and optic nerve. (A. F. I. P. Accession No. 677283, Picture No. 56-23057, × 305.)

nerve fiber layer. A sheet of such cells adhered to the inner surface of the inner limiting membrane and between the footplates of Müller's fibers. Few mitoses were present in the tumor infiltrating the retina. There were no areas of necrosis, hemorrhages, or calcifications and no rosettes. The structure of the retina was preserved in its entirety, and its thickness was not increased greatly by the tumor (Fig. 3). Between the retina and the pigment epithelium a ribbon of tumor cells was present which extended from the region at the optic nerve to near the ora; it was entirely avascular. The cells composing this tumor mass were identical in appearance with those

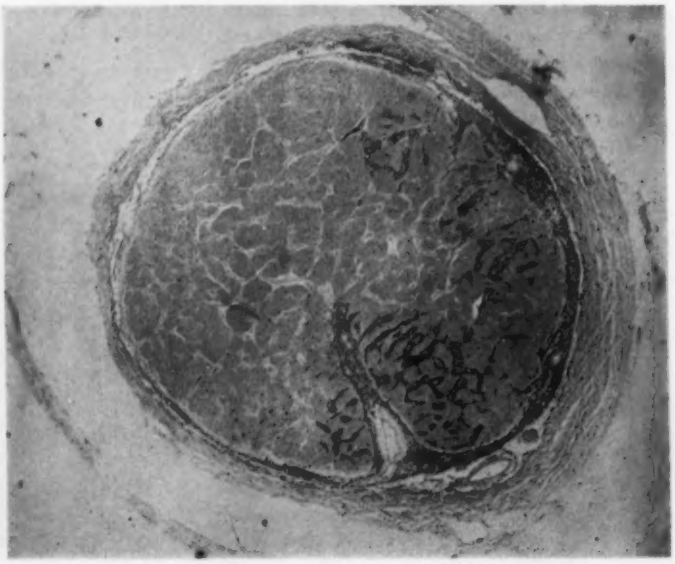


Fig. 6. — Photomicrograph of transverse section of left optic nerve near globe. (A. F. I. P. Accession No. 677283, Picture No. 56-19957, × 22.)

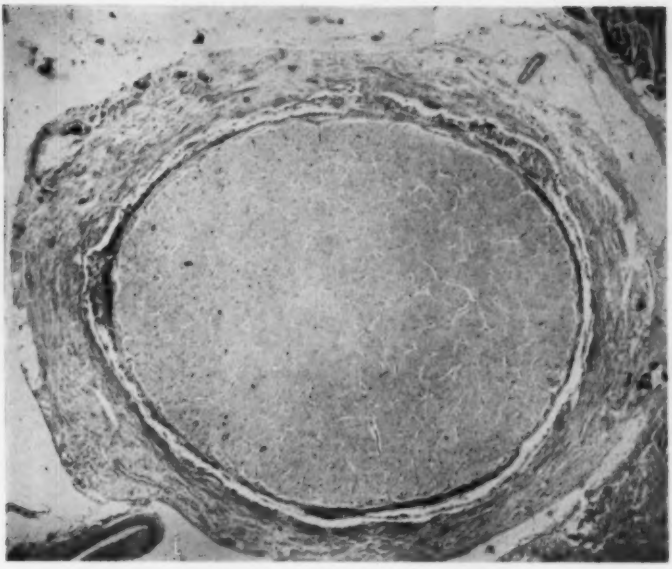


Fig. 7. — Photomicrograph of transverse section of intraorbital segment of left optic nerve, with slight neoplastic infiltration of the pial and arachnoidal sheaths. Nerve substance free of tumor—so-called "jump." (A. F. I. P. Accession No. 677283, Picture No. 56-19955, × 25.)

infiltrating the retina. The optic disc was swollen and densely infiltrated with neoplastic cells, varying considerably in size and shape (Figs. 4 and 5). The connective tissue and the lymph spaces around the central retinal vessels were filled with neoplastic cells. The lamina cribrosa was bent backward, and the tumor infiltration extended undiminished beyond it, causing the nerve to be thicker than normal. The septa of the optic nerve were intact. A few tumor cells were visible on the dural sheath. In the distal portion of the optic nerve, near the point where the vessels enter it, the neoplastic infiltration was limited to the part around the central vessels

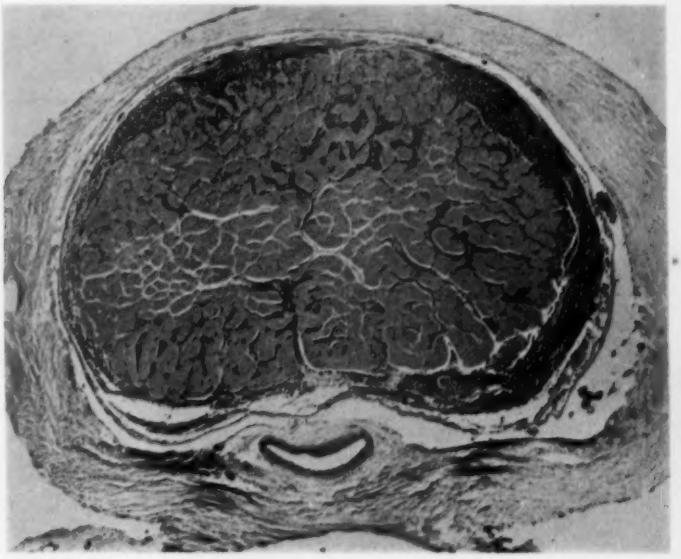


Fig. 8. — Photomicrograph of intracranial segment of left optic nerve. (A. F. I. P. Accession No. 677283, Picture No. 5619959, × 22.)

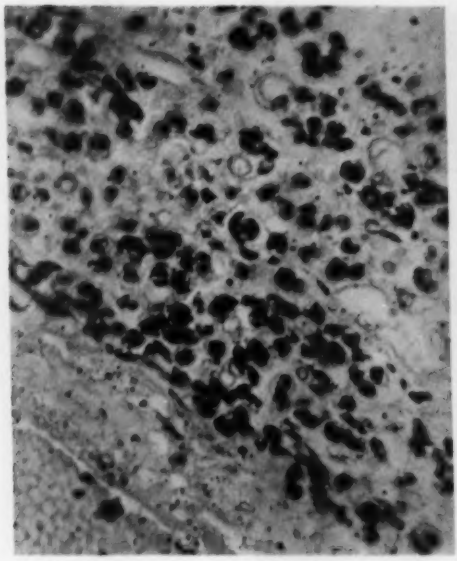


Fig. 9.—Photomicrograph of neoplastic infiltration of leptomeninges, with polymorphism of tumor cells; multinuclear neoplastic cells. (A. F. I. P. Accession No. 677283, Picture No. 55-21186, × 525.)

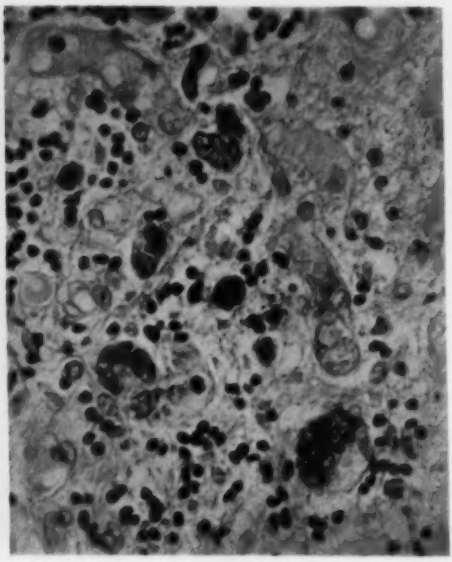


Fig. 10.—Photomicrograph of neoplastic infiltration of brain substance and multinuclear giant cells. (A. F. I. P. Accession No. 677283, Picture No. 55-21183, × 525.)

(Fig. 6). At the apex of the orbit a section of the nerve was free of tumor, but atrophic; its pial and arachnoidal sheath contained neoplastic cells (Fig. 7). In the intracranial section of the nerve the pial and arachnoidal sheaths were very thickened because of the neoplastic infiltration, which extended along the septa between the fascicles of the nerve; there was partial atrophy of the nerve (Fig. 8).

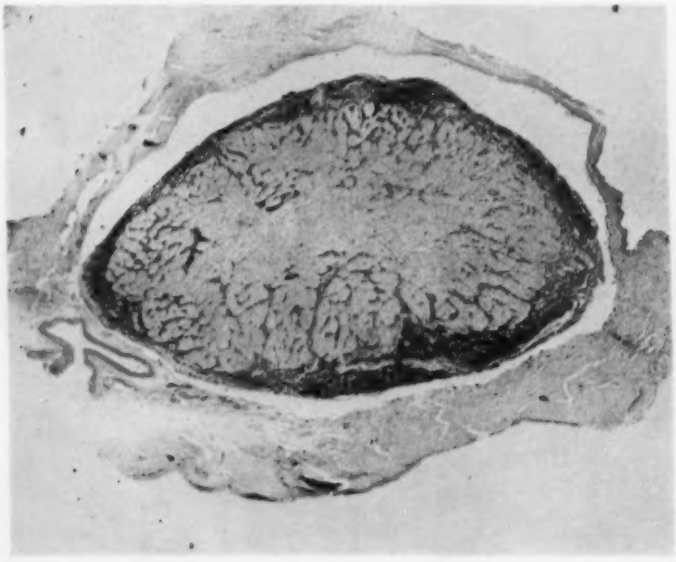


Fig. 11.—Photomicrograph of intracranial segment of right optic nerve with predominantly leptomeningeal neoplastic infiltration and extension into nerve substance. (A. F. I. P. Accession No. 677283, Picture No. 56-19956, × 21.)

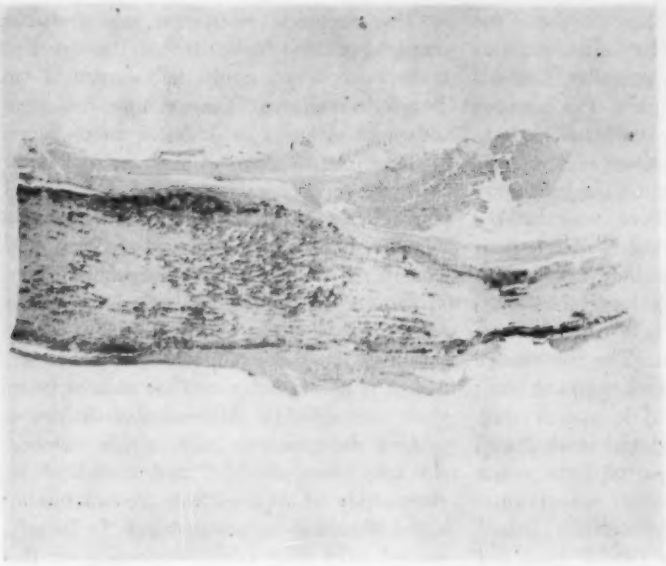


Fig. 12. — Longitudinal section of intraorbital part of right optic nerve, with diffuse neoplastic infiltration. (A. F. I. P. Accession No. 677283, Picture No. 56-19954, ×7.)

Microscopic findings in the brain. A diffuse infiltration of the leptomeninges was present, varying considerably in thickness in different areas. The base and the dependent regions were more involved than the hemispheres. The brain substance was infiltrated superficially with the neoplasm extending either directly from the leptomeninges or via the vessels along the Virchow-Robin spaces. The involvement of the cerebellum and the stalk of the pituitary were conspicuous. The ependyma of the dilated ventricles was covered with tumor cells. Some meningeal vessels were filled with the neoplasm. Within the leptomeninges and the brain substance the neoplastic cells were generally of larger size and different shape, with many multinucleated giant cells among them (Figs. 9 and 10). The infiltration of the cerebellar hemispheres, however, was composed predominantly of the smaller cell type as noted in the retinal tumor. Numerous mitoses were present in the meningeal and cerebral infiltration. The chiasm was intact. The neoplastic infiltration of the meninges extended slightly into the surface.

Right optic nerve. The pial and arachnoidal sheaths of the intracranial part of the optic nerve were heavily infiltrated with neoplastic cells, which continued along the septa into the nerve, in which a small central area was spared (Fig. 11).

The right optic nerve at the apex of the orbit was infiltrated by tumor; here, again, the central part was normal and the neoplastic infiltration was densest around the vessels and septa. The tumor cells exhibited the same polymorphism as was noted in the meningeal and cerebral infiltration. Mitoses were numerous (Fig. 12).

Comment

From a review of the literature of cases of retinoblastoma presenting diagnostic difficulties because of the prominence of iridocyclitic symptoms in the clinical picture, it becomes evident that this case exhibited some other noteworthy features. Precipitate-like corneal deposits, hypopyon-like formation in the anterior chamber, iris nodules described as late metastases of the retinal tumor, and iris atrophy attributed to the glaucomatous state have been de-

scribed in such cases. None of these was present in this patient. The corneal deposits were large, ring-shaped, granular, and not situated in the dependant part. The opacities in the anterior chamber were not a constant finding; their presence was usually associated with a flare-up of the inflammation of the eyeball. There was nothing unusual about them during the early part of the disease, but later they became remarkable because of their large size, whitish color, and intense light reflexion, as well as their slow motion. The iris change was mostly one of color, from hazel to blue; toward the end only did it appear dull. The pupil was not dilated and reacted well to light, without an abnormal light reflex from it. The ocular tension was normal until a rapidly developing cataract caused secondary glaucoma. The fundus remained visible until the cloudy lens interfered. However, there was a disproportion between its visibility and the cloudiness of the media. One felt as if the light directed into the eye was absorbed within it instead of reflected. The optic disc was swollen and of the same appearance as the surrounding retina. Surprisingly, vision of counting fingers was retained until the lens became cataractous. After the cataract extraction the corneal deposits disappeared. Sijpkens[5] considers such an occurrence as indicative of a tumor of the posterior segment, in some cases undiagnosed because of cataract, glaucoma, etc.

In cases of retinoblastoma with predominant involvement of the anterior segment at the later stages, the differential diagnosis has hitherto been concerned with tuberculosis or syphilis. In the case presented here concurrence of an intestinal nematode infestation, a high titer of the dye test for toxoplasmosis, and the great sensitivity to Staphylococcus toxin made the diagnosis difficult. As nematode endophthalmitis and noncongenital toxoplasmosis of the eye are known primarily as pathologic entities, the unusual clinical features of the case were interpreted as caused by the latter.

The nematode infestation was a chance occurrence; the high titer of the dye test for Toxoplasma and the sensitivity to Staphylococcus toxin were only indicative of a past or latent infection of these agents.

The microscopic findings in the enucleated eye explained many of the unusual clinical features. This was a retinoblastoma planum, a term coined by Hirschberg and considered by him a late stage of the initial circumscript form. This seemed to be in agreement with the observation of a single focus in the fundus by the first examiner. When it was seen by me, five months later, there was a diffuse infiltration of the retina around the posterior pole, which included the optic disc. Parkhill and Benedict,[6] in their study of 35 eyes with retinal tumor, noted that the neoplasm most frequently started as a progressive thickening of the retinal layers and replacement of the normal cells by tumor cells like "a malignant transformation in situ." This is a succint description of the microscopic appearance of the retina of this case. As the external nuclear layer was the most heavily infiltrated by the neoplastic cells, it may be assumed that the retinoblastoma originated there. The absence of necroses, hemorrhages, and degenerations was noteworthy and possibly due to a slow progression of the disease.

There was no detachment of the retina; this as well as the absence of a tumor mass proper may explain the lack of an abnormal reflex from the pupil.

The ribbon-like extension of the neoplasm between the retina and the pigment epithelium was probably the cause of the diminished fundus reflex.

The spread of the tumor into the central nervous system occurred through the optic nerve, then along the central vessels with their perivascular tissue to the sheaths of the optic nerve and the meninges. The "jump," absence of neoplastic infiltration in the optic nerve substance beyond the point where the central vessels left the nerve, as well as the appearance of the optic

chiasm, lends support to the supposition that the tumor followed this way into the brain.

The optic disc of the right, uninvolved, eye remained normal clinically, and the vision was 20/20 when examined a few days before death. However, at autopsy the sheaths and the optic nerve itself were found to be infiltrated with neoplasm. Siegrist [7] observed a similar occurrence in one of his cases.

Because of the age of this patient, his good power of observation, and the location of the primary focus near the macula, one is able to assess better than in most cases the duration of his disease. Complaints of visual impairment were made by him 8 months prior to the onset of ocular inflammatory symptoms; the manifest stage lasted 17 months; the last 3 months of his illness were marked by signs of metastases in the central nervous system.

Summary

A sporadic unilateral case of retinoblastoma in an 8-year-old boy went undiagnosed because of atypical clinical manifestations and absence of tumor symptoms.

An intestinal nematode infestation, a high titer of dye test for toxoplasmosis, and a great sensitivity to Staphylococcus toxin further clouded the true cause of the ocular disease.

Some vision was retained till three months before death, when a complicated cataract developed.

Microscopically a diffuse neoplastic infiltration of the entire retina was present, without necrosis, hemorrhages, or degeneration. Early extension into optic disc occurred, but no metastases in the choroid existed.

Polymorphism of the tumor cells was noted in the ocular metastases and was more remarkable in those of the central nervous system.

Death was due to the tumor invasion of the central nervous system from the optic nerve into the leptomeninges.

The optic nerve of the other eye, ophthalmoscopically and functionally normal, was found microscopically to be invaded by tumor.

709 New Medical Bldg.

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Experimental Studies of the Choroidal Vessels

V. Hemodynamic Observations

ENRIQUE WUDKA, M.D., and IRVING H. LEOPOLD, M.D., Philadelphia

The exuberant vascularity of the choroid and its functional significance have been the object of numerous investigations throughout the years. It is certainly remarkable (particularly if it is remembered that the discovery of the circulation by Harvey [1,2] took place in 1628) to find established in the nineteenth century that the function of the choroid "is to nourish the retina through its arteries and veins . . . ." [3]—old indeed are the roots of some of our knowledge.

With relatively few exceptions, most of the further progress of our knowledge of the middle ocular coat has been made through studies of enucleated eyes or by indirect observations in vivo. The aim of the present investigation was to obtain further evidence which might assist in the understanding of the circulation in the choroid through direct observations of its vessels in living animals.

General Methods of Investigation

The techniques used in the study of the choroidal circulation in living animals through the outer ocular coat have been described previously.[4] Presently only a brief summary of the material and methods of investigation is given.

Dehydrated Sclera.—This procedure consists in studying the choroidal circulation through the dehydrated sclera of the proptosed eyes of animals. To render the scleral tissues transparent, the conjunctiva is dissected off the area to be examined. Sutures are inserted in the conjunctival flap that permit holding the eye in the desired position. Bright focal illumination supplied from below allows the choroidal vessels to be examined in detail after dehydration of the sclera develops. This method permits the visualization of large areas of the choroid but has the disadvantage of producing ocular hypotony.

Scleral Window.—This technique consists in dissection of a conjunctival flap followed by a scratch-down incision in the sclera until the choroid is reached. With a spatula the suprachoroidal layer is liberated of fibers, and in the empty space a small transparent plastic plate is inserted. The sclera above the plate is then trephined, thus leaving a round window through which the choroidal vessels can be seen. This type of window permits studies under more physiological conditions but narrows the field of observation considerably.

Procedure.—The work was done primarily in anesthetized albino rabbits, in which the lack of pigment facilitates the direct observation of the choroidal vessels. With either of the described procedures the choroid was studied through a binocular stereoscopic microscope that provides magnifications ranging between × 10 and × 150. Photographs of the material studied were obtained with an Exakta VX camera mounted in a microscopic adapter. Besides the usual black and white pictures it was possible to obtain colored plates.

Combined with these general procedures special techniques were followed that will

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be described in the corresponding sections of this presentation. At least three animals were used in each study.

Type of Blood Flow

Hemodynamics is the study of the manner in which the physical properties of the blood and the vessels through which it circulates affect the blood flow and pressure.

A viscous, or Newtonian, fluid is one in which flow is proportional to the propelling force. In another group, called pseudoplastic or non-Newtonian, the flow rate is proportionately faster as the force causing it to flow increases.

In the larger vessels the blood behaves like a viscous fluid, and the diagram of the relative blood velocity at different points within the vessel is represented by a parabola. In vessels of narrow caliber the blood becomes pseudoplastic; the red cells are concentrated in the axial part of the stream, and the plasma flows along the walls. As a consequence, the red cells circulate faster than the plasma and the effect of the pseudoplasticity of the blood in narrow vessels is to modify the parabolic contour of the velocity distribution curve.[5]

The motion of a fluid may be of two kinds, viz., streamline or turbulent. In streamline motion the filaments move in definite paths, and in turbulent motion the fluid moves in an eddying mass. The nature of the two modes of fluid motion was first demonstrated by Reynolds[6] in a series of experiments with parallel glass tubes of various diameters. He also established the conditions tending to the maintenance of streamline flow.

Observations

The motion of blood in the larger arteries of the choroid (long and short ciliaries) is ordinarily too rapid to be seen with the methods of investigation used in this study. Only when the blood pressure falls to a low level is the flow of blood noted as a uniformly granular red stream.

In a number of arterioles and in the majority of vessels on the venous side of the circulation the motion of blood is visible. It is usually characterized by a central dark stream flanked by two narrow light fringes. Streamline flow is evident by the fact that blood flowing into a collecting vein formed by the union of two or more veins tends to remain in separate streams for some distance before mixing. Such respective streams were traced by observing a central clear flow between two dark columns present in the collecting vessel.

In a few areas streamline flow does not occur; turbulence and eddy currents form at the point of vascular junction, with immediate mixing of the blood of the different vessels. These turbulent areas were noted at the points where deeper veins drain into the superficial ones.

Under some scleral windows the venous flow of some areas seemed to slow down, to pulsate for a few moments, and then to reverse, returning later to its original direction. These changes are probably artefacts produced by the insertion of the plastic, as they were never observed in dehydrated preparations, in which the movement of blood is uniform towards the vortices.

Interference with Arterial Supply and Venous Drainage

In this section reference will be made to the changes induced in the choroidal circulation as a result of: (I) occlusion of the carotid arteries; (II) occlusion of the ciliary arteries, and (III) occlusion of the vortex veins.

I. Occlusion of the Carotid Arteries.—The early studies of Adamük,[7] von Hippel and Gruenhagen,[8] Graser,[9] von Schulten,[10] and others showed that carotid obliteration produces a fall in the intraocular pressure in the homolateral eye. Heine[11] qualified, in his observations, that the decrease in intraocular pressure was not constant.

After carotid ligation or compression in albino rabbits, Kussmaul[12] observed pallor of the iris without a similar involvement of

the fundus. While performing carotid occlusion in dogs, Weber [13] noticed collapse of the vessels in the major circle of the iris. Linner [14] observed in rabbits that ligation of the common carotid diminished by 19% the quantity of blood escaping from an incised vortex vein in the homolateral eye.

Barany,[15,16] using topical anesthesia and tonometry, recorded that unilateral closure of the carotid in the rabbit causes an homolateral fall of 4 mm. Hg in the intraocular pressure and a drop of 30 to 40 mm. Hg in the pressure of the ophthalmic artery. These changes were followed by a return to normal by the intraocular pressure even though the arterial pressure in the ear on the operated-on side remains depressed. Applying a manometric technique, Davson and Matchet [17] found that in normal rabbit eyes unilateral carotid occlusion also causes an immediate fall in intraocular pressure. This decrease averaged 7.5 mm. Hg. Kornblueth and Linner [18] applied tonography to rabbits under general anesthesia. They found that the fall in intraocular pressure on the ligated side amounted to nearly 6 mm. Hg. The rate of aqueous flow and the coefficient of facility of outflow were also decreased in the occluded side.

Siegrist [19] surveyed extensively the literature of the past century on the ocular effects that develop after carotid ligation or compression in man. He mentions the appearance of some transitory decrease in intraocular pressure. Digital compression of the carotid in man was shown by Golowin [20] to cause a 2 to 3.5 mm. of Hg fall in the tension of normal eyes. Swan and Raaf [21] studied cases that were treated surgically by carotid ligation. They noted ocular hypotony that developed within the first hour after operation; 24 hours later the tension varied from 10 to 13 mm. (Schiøtz), and it remained depressed for periods up to six months. Also observed was a 25% to 50% reduction in diameter of the retinal arterial vessels. Becker and Friedenwald [22] state that if the homolateral carotid artery is compressed during tonography there is a precipitous fall in the intraocular pressure tracing.

Method: Observations were made in albino rabbits in which one or both common carotid arteries were dissected in the neck region. A loose tie was placed around the vessel, and the animals were prepared for study of their choroidal circulation. The carotid ligature was tightened while the choroid was microscopically observed.

In a second group of animals the carotid contralateral to the eye to be studied was cannulated with a polyethylene tube. While the eye was under observation contrast media were injected through the tube. These consisted [23-27] in (*a*) methylene blue in a 1% aqueous solution, (*b*) carmine in a 0.5% solution in Gifford buffer, (*c*) light green in a 1% aqueous solution, (*d*) hematoxylin (Mayer's hemalum solution), (*e*) thioflavine S in a saturated aqueous solution, (*f*) carbon black suspension in Ringer's solution (supernatant fluid after standing for several days).

When thioflavine S was employed, observations were made with ordinary light and ultraviolet light. The latter was arranged in a device similar to the quartz rod apparatus suggested by Knisley.[28] * The Purple X-GE (250 watt) bulb employed did not provide sufficient illumination for satisfactory studies.

Observation: Immediately after ligation of the homolateral common carotid there was some narrowing in the long posterior ciliary arteries. The decrease in vessel caliber was somewhat more evident in the intraocular portion than in the extraocular portion of the vessel. Simultaneously slight pallor was noted in the column of flowing blood.

When the contrast media were injected under pressure through the contralateral carotid artery, the dye was noticed to ap-

* Part of the necessary equipment was lent by Dr. S. I. Askovitz from the Ophthalmology Research Laboratory, Albert Einstein Medical Center-Northern Division, Philadelphia.

pear in the choroidal vessels of the eye under observation.

Methylene blue, carmine, and light green produced transitory staining of the larger choroidal vessels, creating a beautiful color change in the entire ocular coat; nevertheless, this staining did not abet the visualization of the choriocapillaries. Thioflavine S and hematoxylin diffused rapidy through the vascular walls, and carbon black did not give enough contrast, and so neither of these agents gave sufficient aid for the delineation of the vascular structures.

Comment: The extracerebral circulation to the head of the rabbit is apparently functionally separated in the two sides.[17] The circle of Willis in the living animal[30] does not permit the interchange of the blood streams in the main vessels across which it lies because of inherent hydrodynamic characteristics.[31] The present studies appear to indicate that blood entering the eye under normal conditions comes from the homolateral carotid artery but that the circle of Willis may be considered as a potential shunt which can be utilized in the presence of vascular obliteration, as was indicated in our studies with coloring materials. The adequacy of the circle as a bypass will depend on the inherent structural characteristics of the individual.

Unfortunately, the dyes employed did not help in the better outlining of the choriocapillaries.

II. Occlusion of the Posterior Ciliary Arteries.—Obliteration of vessels supplying the uvea can be considered to have importance because of (A) the concept of segmentation in the uveal tract with associated vicarious function to maintain viability and (B) the modifications in intraocular pressure induced through alterations in the vascular supply.

A. The classical experiments of Wagenmann[32] created the concept that the vessels within the choroid have a segmental distribution. He found that after section of part of the posterior ciliary arteries in the living rabbit an area of choroidal ischemia and atrophy with pigmented degeneration of the retina developed. These changes corresponded in location to the field of distribution of the affected vessels. Capauner[33] and Kruckmann[34] also found similar alterations after inducing choroidal circulatory disturbances in experimental animals. Following the technique described by Wagenmann, Nicholls[35] repeated the original studies and reevaluated the results. This author found that in order to produce an area of degeneration it was necessary to interfere with at least two-thirds of all the posterior ciliary arteries.

Siegrist[36] studied the individual ciliary arteries after ligation followed by injection of a dye into the carotid. He found that the areas of choroid supplied by individual vessels are not filled by neighboring vascular beds. From these studies he concluded that the ciliary vessels behave as end-arteries. On the other hand, Bossalino[37] concluded that obliteration of an isolated artery produces nutritional alterations that are completely restored through the collateral circulation.

The description of the choroid by Leber[38] has been interpreted as favoring the concept of segmental distribution of the vascular supply in this ocular coat. According to him, the short posterior ciliary arteries in the midchoroid of human eyes anastomose usually only to a slight degree but extensive anastomoses are present in the corresponding capillary bed. The lack of arterial anastomotic branches does not apply to the vicinity of the optic nerve and the periphery of the choroid, where the posterior ciliaries anastomose with the recurrent branches from the major circle of the iris. The choroid of rabbits injected with plastic material was studied by Vilstrup.[39] She found that the short ciliary arteries anastomose more abundantly than has been described in the literature, but no anastomoses were found between them and the recurrent arteries of the major circle of the iris. On the basis of the course and distribution of the ciliary arteries, Vilstrup considers the

choroid divided into three regions that lack sharp demarcation.

After operative obliteration of ciliary vessels in opticociliary neurectomies, Schlodtmann,[40] Studer,[41] Coats,[42] and others observed changes in the retina and choroid that were attributed to an interference with the blood supply. In an eye enucleated following retinal detachment surgery, Wilson and Irvine [43] found necrosis of uveal tissue that was imputed to the destruction of the ciliary arteries.

Clinicopathologic studies were reported by Coats [42,44] of cases that showed a quadrangular patch of choroidal atrophy. He concluded that the changes present could best be explained by an obstruction of a posterior ciliary artery, with consequent infarction of the inner layers of the sclera, the choroid, and the retina.

On the basis of clinical studies, Hepburn [45] suggested that the posterior ciliary vessels behave like a terminal vascular system. In cases of deep choroiditis he found wedge-shaped scotomata in the field of vision extending into the extreme periphery and having no relationship to the size of the original focus. He concluded that the loss of a sector of retinal function was caused by the cutting off of its vascular supply. Feigenbaum and Kornblueth [46] published a similar case.

Wybar [47] prepared casts of the choroid by intravascular injections and observed that the short posterior ciliary arteries were segmentally arranged. Each branch supplies a localized area of the choroid, but there was no anatomical evidence for the concept that these arteries were true end-arteries. This author surveyed the theories of division of the choroid into sectors and zones and offered different explanations for the clinical cases which have been cited to illustrate the existence of choroidal segmentation.

B. Wagenmann [22] reported transitory ocular hypotony in rabbits when some of the posterior ciliary arteries were obliterated. Coagulation of a single long posterior ciliary artery was found by Guerry [48] to reduce the intraocular pressure in both the rabbit and the human for a period of about two weeks. Angiodiathermy in man was carried out on the nasal vessel, which is more prominent and can be more easily identified, while the temporal artery is usually obscured by the attachment of the inferior oblique muscle. The procedure was suggested to be employed in combination with cyclodiathermy. It was considered safer than posterior sclerectomy and useful for preventing initial tension rise that often follows cyclodiathermy.

Based on the same general principles, namely, the relief of ocular hypertension through reduction of blood supply, several procedures have been evolved for the therapy of glaucoma.

In the technique employed by Schulte [49,50] obliteration of the long posterior ciliary artery is attempted. The nasal artery was selected, as it is larger and more accessible. This vessel perforates the sclera 13.4 mm. from the limbus, while the temporal artery enters 19.2 mm. behind the limbus. Obliteration of one vessel was not sufficient for control of pressure in cases of glaucoma, and additional coagulation in the area of the ciliary body had to be done. Biozzi [51] performed angiodiathermy of a long posterior ciliary artery to obtain an antiglaucomatous effect and was able to observe the thrombosed vessel by ophthalmoscopy.

Schreck's [52,53] method is intended for coagulation of the long posterior ciliaries by anolysis (ciloanolysis). He inserts an electrode similar to a cyclodialysis spatula in the suprachoroidal space 7 to 8 mm. from the limbus. The long posterior ciliaries run forward at the level of the horizontal meridian, and the spatula crosses their route immediately behind the ora serrata. This operation when combined with cyclodialysis is known as cilocycloanolysis.

Diathermic occlusion of both long posterior ciliary arteries behind the insertion of the horizontal recti is performed by Ketesy [54,55] (cycloanemization). The operation was effective particularly in cases of glaucoma where the tension lies between 30 to 40

mm. Hg. It is considered an efficacious procedure when used as a complement to other antiglaucomatous operations, in particular cyclodialysis. A slightly modified technique was tried successfully by Stergar [56] for cases of primary chronic glaucoma. Bietti [57] considers that the action of the procedure is at least partially similar to that exerted by nonperforating cyclodiathermy, even if an occlusion of the terminal branches of the long posterior ciliaries occurs simultaneously.

Arato [58-62] recommends obliteration of the long posterior ciliary and the anterior ciliary arteries by diathermy puncture over the scleral insertion of the horizontal recti in order to reduce the formation of aqueous. By means of a 1.5 mm. needle two rows of punctures are made in the area before the muscle insertion. The punctures of the first row go immediately parallel to the insertion; those of the second row, 1 to 2 mm. toward the limbus, in front of the interspaces of the punctures of the first row. On the basis of results of 100 operations the author states that the procedure brings lasting normalization of the tension in cases of simple glaucoma. In the absolute stage of glaucoma and in the presence of an ocular tension higher than 45 to 50 mm. Hg it is less effective. Knobloch [63] also performs angiodiathermy immediately in front of and parallel to the insertion of the lateral and medial recti. He recommends the procedure for cases of simple glaucoma.

Occlusion by diathermy of all the anterior and one posterior ciliary arteries is suggested by Albrich [64] for the treatment of glaucoma. This author recommends that when the long ciliaries can not be found the overlaying sclera should be sectioned, forming a pedunculated flap that permits the proper exposure of the vessel. This technique has also been tried by Fleischer.[65] By exclusive diathermy coagulation of the anterior ciliaries, Baurmann [66] did not obtain permanent favorable results.

Method: Observations were made after obliteration of the extra- and intraocular portions of the long ciliary arteries, the short ciliaries, and their branches.

I. The extraocular portion of the long posterior ciliary arteries was exposed by dissection of the conjunctiva and rotation of the eye. The vessels were localized slightly below the horizontal meridian of the globe; a double-armed nonabsorable surgical (silk) suture was passed underneath them and tied. The arteries were sectioned between the two sutures. The animals were studied immediately and one week after one or both arteries had been cut.

II. Occlusion of the intraocular portion of the long posterior ciliaries, the short ciliary arteries, and their branches was accomplished by surface diathermy application on the vessels under direct visualization through a microscope. The current was applied as long as was necessary to obtain a complete interruption of the blood flow.[67]

Observations: I. (*a*) Immediate circulatory changes. After section of the extraocular portion of one long posterior ciliary artery variable circulatory modifications occur that depend on the individual anatomic arrangement of the choroidal vessels. The portion of the vessel distal to the ligature undergoes a decrease in caliber accompanied by alteration in the direction of blood flow. The circulation is retrograde; it usually comes from the terminal branches and occasionally also from some of the collateral short ciliaries. This retrograde flow of blood proceeds from the long to the short ciliaries, where the direction of blood maintains its normal course. The reversed column of blood is lighter in color and shows a slower speed of movement. The walls of the larger vessels through which it traverses acquire a white brilliant appearance. Complete stagnation of blood is present in the portion of the vessel that does not have a collateral branch for the escape of blood, and it acquires a dark purple color. There is a general slowdown of circulation in the neighborhood of the ligated vessel; complete stagnation or reversal of flow develops in

some arterioles and venules. "White emboli" were observed and carried away in the circulation.

When the second long posterior ciliary artery was ligated, several changes occurred in the described picture. In some vessels the direction of flow remained unchanged; in others the movement of blood reversed to an abnormal or to the original direction, and still other vessels acquired an alternate flow until the column of blood completely stopped. In some vortical areas the direction of flow is normal in the posterior branches and reversed in the anterior ones.

The whole of the choroidal circulation undergoes an adaptation for the purpose of conveying blood from the posterior unaffected ocular segment into the anterior portions where the arterial supply has been interrupted. This is accomplished in some areas at the expense of creating an abnormal retrograde flow from the veins, through the capillaries, and into the arterial side of the vascular bed. In the areas where the vessels carry this vicarious function the column of blood appears paler, has a slow motion, and has a great tendency to undergo complete stasis in some points.

(*b*) Circulatory changes after one week. Observations made one week after the obliteration of a single long posterior ciliary showed slight narrowing of the intraocular portion of the vessel. The blood flow is reversed, being directed toward the ligated point. Through this circulatory arrangement the branching short ciliaries arising from the main trunk receive a blood supply that has a normal direction. Although the appearance of the column of blood in these vessels is improved (as compared with its appearance shortly after ligation), there still is a greater than normal tendency for the development of stasis.

One week after obliteration of both long posterior ciliary arteries the anterior ocular segment revealed marked degenerative changes (Wagenmann,[32] Siegrist,[36] Guerry,[48] Vilstrup,[39] and others). Dehydration of the sclera for the study of the choroidal vessels was poorly accomplished. The few areas observed showed veins of a pale color and a slowly moving column of blood that had a great tendency for stagnation.

II. When the intraocular portion of one long posterior ciliary artery was occluded distally to the point where the short ciliaries originate, the column of blood was seen to move from one terminal branch into the other. In the segment between the occluded point and the terminal branches only a slight to-and-fro movement was observed in the stagnant column of blood.

The application of a diathermy point to a short ciliary artery or to an arteriole induced the same basic circulatory changes. These were characterized by the passage of the column of blood through the anastomatic arterial branches, accompanied on occasions by a reversal of the original direction of flow. Also frequently observed was a retrograde flow from the capillary bed through the main arterial trunk into the collateral branches. The vascular segment between the occluded point and the nearest collateral contained a stagnant column of blood that acquired a reddish purple hue. An infrequent occurrence after the application of a diathermy point was the collapse of a whole vessel, with its branches becoming almost invisible. This type of behavior was more commonly observed in the smaller arterioles.

Comment: The effects induced by occlusion of the ciliary arteries and their branches on the choroidal circulation appear to depend on the quantitative involvement of the vessels.

(*a*) Minimal Occlusion. From the previous description it is evident that the collaterality in the choroidal vascular bed is sufficiently abundant to protect the ocular coat from damage as a result of an isolated vascular occlusion. The choroidal vessels do not form structural end-systems in the true sense. Retrograde capillary flow indicates that there are at least extensive capillary anastomoses between the territories supplied by neighboring choroidal arteries.

(*b*) Moderate Occlusion. When a moderate number of arteries are occluded, the circulation is not completely abolished in the affected region. The blood is carried to the involved areas either through interarterial anastomoses or by retrograde flow. Initially the flow of blood is decreased, but later the blood column acquires an appearance that closely mimics the one present under normal circumstances. During the period required for the circulatory adjustment to develop, metabolic and hydrostatic changes may appear. As a consequence, transitory and even permanent changes may occur in the ocular coats, affecting areas of variable size. The hydrostatic reversal will manifest itself by a tendency of the tensional characteristics of the eyeball to return toward the original.

The interpretation of the functional significance of collateral connections demonstrated by injection techniques should be guarded. These techniques show that collaterality exists, but they do not give satisfactory evidence that the collateral channels are functionally operative at levels required to maintain viability in the structures involved.

(*c*) Extensive Occlusion. With an extensively involved arterial supply, irreversible changes will occur in the structures of the eye nourished normally by the affected vessels.

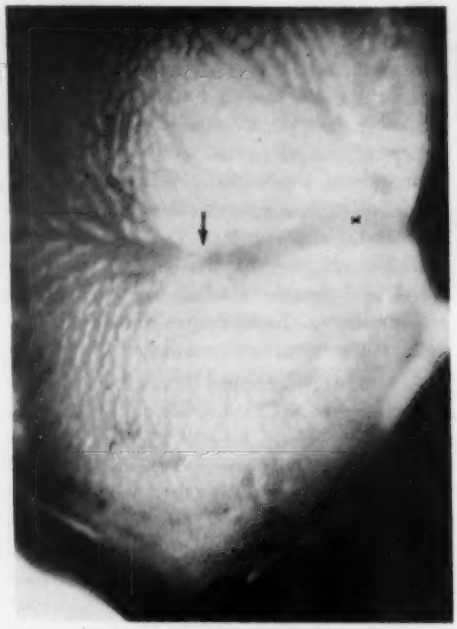
III. Occlusion of the Vortex Veins.—Experimental ligation of the vortex veins has been performed by numerous investigators. These observations were undertaken primarily for the study of the characteristics of the venous circulation and its relations to other functional activities in different structures of the eye (Adamük,[68] Leber,[69] Weber,[70] Schoeler,[71] Arlt,[72] von Schulten,[10] Ulrich,[73] Koster,[74] van Genus,[75] Weiss,[76] Magitot,[77] Duke-Elder,[78] and others). The changes described after ligation of the superior vortex veins involve an immediate hyperemia of the iris in the segment drained by the veins. This is accompanied by a rise of tension of about 20 mm. Hg. If ligation of the inferior vortex veins is then performed, intraocular pressures up to 80 to 90 mm. Hg have been readily induced. At the same time, the anterior chamber becomes shallow, the pupil dilates, and marked hyperemia develops in the iris. There is formation of a colloid-rich plasmoid aqueous and marked engorgement of all the vessels throughout the fundus. Later the cornea becomes opaque, the tension remains elevated, and further ophthalmoscopic studies are impossible. In the course of a few weeks the pressure returns to normal.

A number of clinical studies have been published in which obstruction of the efferent veins is discussed. Reports of this nature were made, among others, by Birnbacher and Czermak,[79] Heerfordt[80,81] Thomsen,[82] Seefelder,[83] Larsson,[84] Black,[85] and Pillat.[86]

Method: The vortex veins were localized and dissected on either side of the superior and inferior rectus muscles. Obliteration of the vessels was accomplished by a double silk tie placed around them; they were then sectioned between the two ligatures. A variable number of veins (from one to four) were tied in each animal, and observations were made immediately and one week later.

Observations: (*a*) Immediate circulatory changes. After ligation of a single vortex vein there is deviation of blood flow into the neighboring areas that is accomplished through a reversal of circulation in some of the choroidal veins. The phenomenon is not generalized, as part of the veins tributary to the affected vortex will remain with a normal direction of flow. When the normally directed column of blood arrives at the ligated vortex it is returned through the tributary veins, in which the direction of flow has been reversed. Simultaneously with these changes it was noticed that the column of blood acquired a deeper color without a noticeable increase in the transverse caliber of the vessels.

As the vortex veins were ligated successively other modifications were observed in



Choroidal veins in living rabbit. After a tie was removed from the vortex vein (*X*), numerous white emboli were noticed. An embolus was photographed at a point distal from the vortical sinus (arrow); reduced from mag. × 10.

the choroid. These consisted in complete stagnation of blood in some veins, with general slowing of the circulation. Reversal of flow partially involved the arterial side of the vascular bed, and in some arterioles and venules near the capillaries a pulsating back-and-forth movement of blood was noticed. The development of thromboses was favored, and the choroidal vessels acquired a deeper tone. Numerous reddish points appeared in the intervascular spaces, and later larger areas of choroidal hemorrhages were identified.

The previous modifications became most dramatic when the last of the vortex veins was tied. Partial return to normal circulatory conditions was noticed when the tie around the vortex veins was removed. This maneuver was sometimes accompanied by a shower of "white emboli"[4] that escaped through the lumen of the open vessel (Fig.).

(*b*) Circulatory changes after one week. Observations made one week later revealed in general that the changes described above persisted. In the areas drained by the ligated vortex veins, reversal of circulation was present in some of the tributary vessels, with deviation of flow towards the neighboring regions. The column of blood in the veins appeared of a slightly deeper color, and the edges of the vessels had in some areas a scalloped appearance. The indentations normally present at the arteriovenous crossings were more accentuated. The openings through which the underlying tributary venules drain into the larger outer veins were distinctly outlined, and at these points the flow of blood had a definite turbulent appearance.

When degenerative changes occurred in the eyeball after ligation of three or four vortex veins, dehydration of the sclera following the usual technique was poorly accomplished and observations were unsatisfactory.

Comment: Occlusion of the choroidal veins will produce a pattern of circulatory changes that *mutatis mutandis* will resemble or even surpass the adaptation that follows arterial occlusion. The venous circulation appears to be in a more favorable condition of adaptation because of the numerous anastomoses present among the larger choroidal veins.

Effect of Increased Intraocular Pressure

The study of artificially induced ocular hypertension has a dual significance: A. By covering the eye into a natural sphygmomanometer indirect measurements of vascular pressure in the intraocular vessels have been attempted. B. It permits determination of the conditions required for the maintenance of a continued circulation within the globe under abnormally high intraocular pressure.

A. The intraocular pressure can be raised either by forcing a fluid into the eye (manometric method) or by pressure applied externally to the intact globe (tonometric method). The behavior of the intraocular vessels has been studied, and the

points of maximal oscillation and absence of oscillation taken, respectively, as the diastolic and systolic pressures (indirect technique for measurement of vascular pressure in the intraocular vessels). These changes can be determined in two ways: (*a*) by the oscillatory method, in which the amplitude of the oscillation is observed in the column of a manometer or the lever of a tonometer, and (*b*) by the ophthalmoscopic method, where the pulsations of the intraocular vessels are seen with an ophthalmoscope. The subject as a whole was extensively surveyed by Duke-Elder,[78] who accompanied his study by a critical review. The manometric technique has found application primarily in experimental animals, while the tonometric procedure has been adapted for clinical use. The latter was particularly developed by Bailliart,[87,88] who popularized a more accurate technique. In this method the intraocular pressure is raised artificially by applying pressure to the outside of the globe with a piston working against a standardized spring (ophthalmodynamometer). The apparatus is placed in the region of the external rectus and while this is done the vascular pulsations in the fundus are observed with an opthalmoscope.

Duke-Elder [78] pointed out that determination of pressures in the intraocular circulation by opthalmodynamometry involves a number of fallacies and that the results obtained have a comparative but no absolute significance. Koch,[89] after reviewing the subject, concluded from the reports in the literature that the technique does not permit us to arrive at definite values of retinal blood pressure. While admitting some of its limitations, Franceschetti, Streiff and Monnier,[90] Redslob,[91] Bailliart,[92] and others consider the method to furnish values with sufficient approximation to make it a useful procedure.

B. Hill and Flack [93] demonstrated experimentally that when they divided a vortex vein of a cat and then allowed it to bleed the hemorrhage was stopped only when the intraocular pressure was raised almost to the level of the carotid pressure. Hill,[94] Starling,[95] and others showed that the intraocular and venous pressures go together; if the former is elevated the latter will increase concomitantly. On raising the intraocular pressure by tonometry, Duke-Elder [78] showed that the intraocular venous pressure rose coincidentally but remained slightly higher than the chamber pressure. These experimental findings were in complete accord with the theoretical requirements necessary in order to maintain continued circulation of blood in an enclosed system like the eye. It is an essential postulate for the maintenance of a continuous circulation that the arterial pressure should be higher than the capillary pressure, the capillary higher than the venous, and the venous higher than the intraocular. If the pressure in the eye is raised, the veins at their points of exit tend to become obliterated. When this occurs, pressure from the arteries increases, causing the veins to reopen, and the circulation will proceed at a higher level. This process can be maintained until the level of pressure in the ophthalmic artery has been reached.

Investigation of the cerebral circulation during periods of increased intracranial pressure was made by Wolff and Forbes.[96, 97] They observed the pial vessels directly through a transparent cranial window, while the cerebral spinal fluid pressure was being raised. These authors considered that three important physiological mechanisms are involved in the maintenance of cerebral circulation under these abnormal conditions. First, the circulation is initially adjusted by means of pressure changes in the vessels that lead to an increase of arterial pressure within the skull. This establishes a slower yet effective circulation through the brain without any rise in systemic arterial pressure. Second, in response to cerebral anemia when the first adjustment is no longer adequate, there occurs a rise in pressure in the systemic arteries. Third, there is a reduction in vascular tone associated with asphyxia which favors the flow of a greater

volume of blood through the cerebral vessels with less resistance than before.

Dobree [98,99] investigated the compensatory circulatory changes in cases of glaucoma. He studied the modifications in caliber of the ciliary and retinal vessels when the tension was high and again after it had been lowered. His observations led him to conclude that when the ocular tension rises two compensatory mechanisms may function together. First, in the more moderate degrees of ocular hypertension the local rise of both the intraocular venous and arterial pressures would seem to be sufficient to overcome the circulatory embarrassment and maintain adequate blood flow. Second, in the higher ranges of ocular tension dilatation of the intraocular vessels becomes increasingly important, because a very small increase in caliber would be sufficient to lower the vascular resistance and greatly to improve the ocular circulation.

Method.—To elevate artificially the intraocular pressure in rabbit eyes a simple manometric apparatus was employed. A mercury manometer with a regulating pressure bulb was connected to a container filled with saline. Through the inlet of the container pressure is transmitted to the fluid, and by the outlet it is allowed to escape through a needle inserted into the anterior chamber.

The choroidal circulatory changes were observed through the microscope while the intraocular pressure was being raised. The values expressing the levels of intraocular pressure do not have an absolute significance but are useful as landmarks indicating a succession of events.

Observations.—With gradual elevation of the intraocular pressure the sequence of vascular events was characterized by the following changes. Slight pallor developed in the area of the venous vortices when the pressure was between 30 and 40 mm. Hg. Pulsations appeared in the posterior ciliary arteries at the points of perforation of the sclera at an average pressure of 79 mm. Hg and acquired maximal amplitude when the level of 83 mm. Hg was reached. Following this, the influx of blood into the choroid was intermittent, and at a pressure of 93 mm. Hg there was a definite decrease in the speed of blood flow. Complete collapse of the intraocular portion of the posterior ciliaries occurred at a pressure level of about 105 mm. Hg. At higher pressures the movement of blood was reversed in the arteries and followed its normal direction in the veins; under these conditions the columns of blood were extremely pale and moved very slowly. The latter changes probably indicate that the blood accumulated in the choroid was being expressed by the increased intraocular pressure through all available channels. Complete standstill of circulation occurred at pressures of 110 mm. Hg or higher.

The progressive changes previously described followed a reversed sequence when observations were started at a high intraocular pressure that was gradually lowered.

Comment.—From the previous description it is evident that when the intraocular pressure is increased in a rather short period of time (up to half an hour) the circulation in the choroid is adjusted by means of pressure changes. The increased ocular pressure is transmitted to the veins; that in turn affect the capillaries and then the arteries. This results in the establishment of a choroidal circulation at a higher level. If the ocular pressure increases further, the process repeats itself until the available force from the arteries is exhausted.

During the present investigation no active or passive dilatation of the choroidal vessels was observed that through lowering the vascular resistance would facilitate the blood flow under conditions of increased intraocular pressure. The lack of a vasodilator response in the choroidal vessels has been discussed in a previous paper.[4]

Summary

Hemodynamic characteristics of the choroidal circulation were studied in living albino rabbits.

The motion of blood in the larger arteries of the choroid is ordinarily too rapid to be seen. The arterioles and veins have a streamline type of blood flow. At the points where deeper veins drain into the superficial ones eddy currents are present.

Ligation of the homolateral common carotid produces some narrowing of the long posterior ciliary arteries. When contrast medium was injected through the contralateral carotid the dye appeared in the choroidal vessels of the eye under observation. The dyes employed did not abet the better visualization of the choriocapillaries.

Occlusion of the ciliary arteries and their branches was followed by compensatory circulatory changes. These consisted in the flow of blood from the anastomotic channels or from the choriocapillaries towards the obliterated vessel. The results obtained are discussed in relation to the extent of the vascular occlusion.

Occlusion of the vortex veins induced modifications in the direction of blood flow in the affected areas.

Artificially increased intraocular pressure produced initially marked pulsations in the posterior ciliary arteries at the points where they perforate the sclera. At higher pressure levels there was intermittent flow of blood and decreased speed of circulation until complete vascular collapse resulted. No active or passive dilatation of the choroidal vessels was observed.

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CORRECTION

In the article "Office Management of Glaucoma," by Dr. W. Howard Morrison, in the August, 1957, issue of the ARCHIVES, two lines of type were printed in wrong locations. The second and third sentences of the section "Ophthalmoscopic Examination" (p. 227) should read: "A description of the fundus and a classification of the papilla are not as accurate nor as useful means of comparison in a prognostic sense as are successive sketches and measurements. The need of periodic study of the eyegrounds necessitates the temporary discontinuance of the use of miotics, particularly if the miosis is marked and the media are hazy." The sixth, seventh, and eighth sentences of the paragraph "Physostigmine (Eserine)" (p. 230) should read: "This increased pressure is very soon offset by the miotic effect. Long-continued blepharospasm takes place. Physostigmine is a vasodilator and, as a result, an increased use of physostigmine frequently causes a follicular conjunctivitis."

The following article was originally published in the September issue. Through an error one page of illustrations in color was omitted. The entire article is therefore being republished.

The Vitreous

Gross and Microscopic Observations Seen in Age and Disease, with Special Emphasis on the Role of Vitreous in Detachment of the Retina

JOSEPH A. C. WADSWORTH, M.D., New York

Introduction

There are relatively few studies of the vitreous found in the literature where emphasis is placed on the gross appearance. Many criticisms of existing studies have frozen further investigation of obvious pathologic changes seen clinically, macroscopically, and microscopically. De Wecker [1] accurately described the process of vitreous shrinkage as well as the important relationship of the vitreous to detachment of the retina. Not until Gonin [2,3] applied cautery to seal the retinal tears did the significance of vitreous changes in retinal detachments finally gain its relative importance.

The normal vitreous is a transparent gel that completely fills the posterior part of the eye. In its normal state it acts as a cushion to help keep the structures of the eye in their normal position. The important function of cushioning the retina helps maintain the retina in contact with the pigment epithelium. In the young adult in whom there has been no history of disease, the vitreous has its normal characteristics. However, with age certain changes take place in the form of shrinkage, liquefaction, and formation of strands. Such changes in themselves may have no adverse affect on the general health of the eye. On the other hand, certain relatively minor changes associated with the usual senescent developments may result in serious complications.[4-8]

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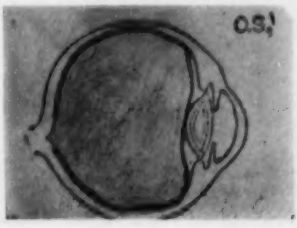
Changes in Vitreous

During the process of opening the globes sent to the Pathology Laboratory at the Institute of Ophthalmology, Presbyterian Hospital, it was observed that certain changes found in the vitreous fell into a general pattern, depending on age, history of ocular disease, or injury. These changes found in the vitreous have been previously described by many authors [9,10]; however, their relative importance has been minimized, since they have often been considered artefacts.[4-8] Further study and research led to the conclusion that most of the changes found were not artefacts but, for the most part, existed prior to enucleation.

A series of normal globes from young persons was opened, both in the fresh state and after fixation. Both the fresh and fixed globes, when opened, showed the vitreous to be transparent, normal in consistency, and at all times filling the vitreous cavity (Figs. 1, 2, 3, 4, 5, and 6).

Other globes, in which there had been a history of disease, when opened, showed typical changes in the vitreous that cor-

Fig. 1.—Diagram showing the normal relation of the vitreous to the other structures of the eye. The vitreous is lightly shaded, and the retina is a dark line. Here, the vitreous completely fills the vitreous cavity and mechanically cushions the retina against the pigment epithelium.



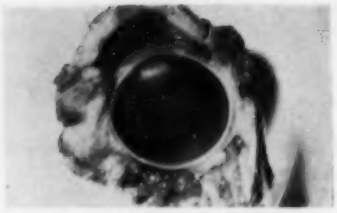
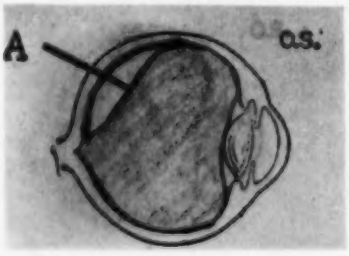


Fig. 5.—A picture of the orbital contents removed because of a malignant melanoma of the conjunctiva. The eyeball is normal. The vitreous is clear and retains its normal consistency.

responded to the type of ocular disease. Where there had been a perforating wound that extended into the vitreous cavity, it was generally possible to follow the course of perforation by a condensation and a loss of transparency of the vitreous. The course of an intraocular foreign body could often be traced by the thin line of opaque vitreous extending from the point of entry and coursing to the locale of the foreign body. In such a case, where there has been damage to the vitreous by the perforating wound or intraocular foreign body, the vitreous becomes liquefied and often leaves localized areas of condensation in the form of dense vitreous strands (Fig. 7). If there has been an associated inflammation, the strands become cellular and later contract. The contracture of the strands often results in a detachment of the retina.[17-19]

In order to interpret many of the routine changes found in the vitreous, it is necessary to study the eye both in youth and in age, because typical changes take place in the vitreous of elderly patients. As previously shown, normal young adult eyes were found

Fig. 8.—Diagram showing an early detachment and shrinkage of the vitreous (*A*). The superior detachment is the earliest change and is usually limited by the ora and optic nerve.



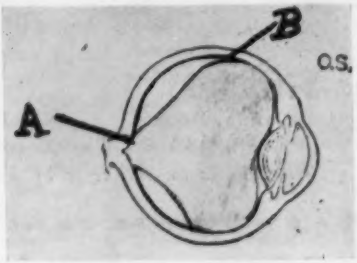
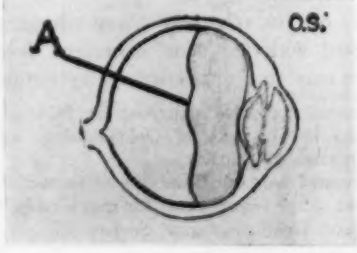


Fig. 9.—A diagram showing a somewhat more advanced shrinkage of the vitreous. However, the vitreous is still attached at the optic nerve (*A*) and near the ora (*B*).

to have normal vitreous. However, with age, there is a tendency for vitreous to shrink and become detached posteriorly.[20-26] The superior portion of the vitreous is usually the area to become detached earliest (Fig. 8). The posterior hyaloid is often visible with the slit lamp clinically. With subsequent shrinkage of the vitreous, the space created between the retina and the hyaloid is filled with a fluid substance resembling aqueous. Further detachment of the vitreous extends to the region of the equator, but the attachment of the hyaloid to the optic nerve remains (Figs. 9 and 10). The attachment of the vitreous to the optic nerve subsequently separates, and there is then a complete posterior detachment of the vitreous (Figs. 11, 12, 13, and 14).[27,28] Oftentimes, such a detachment can be seen clinically and is identified by the presence of a circular opacity undulating on the posterior surface of the hyaloid.

In the absence of previous ocular disease, such shrinkage of the vitreous may cause no

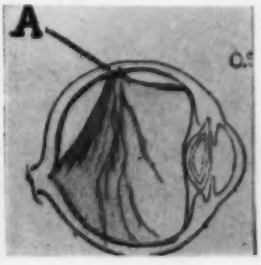
Fig. 11.—A diagram showing complete posterior detachment of the vitreous (*A*). Progressive shrinkage of the vitreous has caused detachment of the hyaloid from the optic nerve.



damaging effects to the eye. When the vitreous first becomes detached, however, there are symptomatic manifestations in the form of lightning flashes. This was first described by Moore [29] and later amplified by Verhoeff.[30] The symptoms were explained by the fact that the floating vitreous strikes against the retina following rapid movement of the eye. Such contact with the retina causes stimuli, to be interpreted as lightning flashes. Further shrinkage of the vitreous results in a disappearance of these troublesome symptoms.

Detachment of the vitreous is an extremely common finding in patients over 50 years of age. Above the age of 65 years shrinkage of the vitreous was found in between 70% and 75% of the eyes examined. Simple shrinkage of the vitreous cannot be associated with other pathological changes found in the eye, but it is apparent that some conditions in the eye may hasten or cause changes identical with those seen in the elderly person. In cases of myopia a shrinkage and liquefaction of the vitreous may develop and numerous floating strands are often seen clinically as well as macroscopically. These changes per se may cause no damage to the visual organs. However, if in the process of shrinkage there exists an adhesion of the vitreous to the retina, subsequent shrinkage of the vitreous may result in a retinal tear following traction on this localized area [32] (Fig. 15). Condensation of the vitreous with or without downgrowth of cellular elements along the strands

Fig. 15.—A diagram showing superior detachment and shrinkage of the vitreous with the presence of a retinovitreous adhesion (*A*). There is obvious traction exerted by the vitreous on the retina.



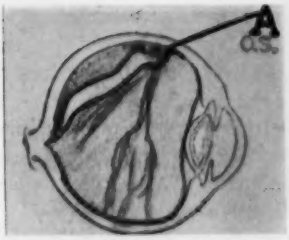


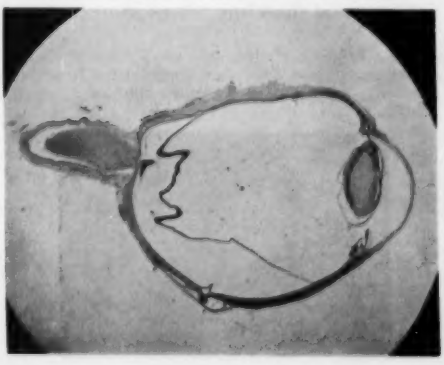
Fig. 16.—A diagram showing a situation similar to that in Figure 15 but with further shrinkage of the vitreous and a tear in the retina at the point of retinovitreous adhesion (*A*). Once the tear is present, fluid migrates behind the retina and causes a detachment of the retina. The subretinal fluid is darkly shaded.

may subsequently contract and cause sufficient traction on the retina to create a tear and later cause a detachment (Fig. 16). From the above facts, it can be concluded that the vitreous plays a dominant role in the formation of detachment of the retina.[33] Such details can be clearly seen by studying the specimen shown in Figures 17, 18, 19, and 20.

The patient is said to have developed a detachment of the retina involving the superior temporal quadrant. A horseshoe-shaped tear was found and treated with diathermy. On or about the second week, there was noted an elevation of the treated area, and, in addition, the region had a bluish-gray color. A neoplasm was suspected, and an enucleation was performed.

Examination of the globe showed the treated area of the sclera to be markedly

Fig. 19.—A photograph of the microscopic section taken through the region of the tear. The marked flattening of the sclera is obvious.



flattened (Fig. 17). When the globe was opened no tumor was found, but there was a moderately severe hemorrhage in the choroid. The retina was in place, and the area of treatment completely surrounded the tear. The vitreous was detached and shrunken but was adherent to the tear (Fig. 18).

After studying the illustrations in this case, it may be surmised that the apparent elevation was due to the fact that the sclera was shrunken and flattened, giving the ophthalmoscopic appearance of elevation (Fig. 19). The bluish-gray color was no doubt due to the choroidal hemorrhage (Fig. 20).

In spite of the ophthalmoscopic changes, the retina had been reattached and the hole had been sealed by diathermy. After treatment, the vitreous continued to remain attached to the flap of the retinal hole.

During life, small areas in the retina become atrophic. The cause of these changes is not clear, but at these points of atrophy the vitreous becomes adherent. During the process of detachment and shrinkage of the vitreous with progressive age these localized adhesions may exert traction on the thin, atrophic area of the retina, causing a tear, with subsequent detachment of the retina (Fig. 21).[34]

In addition to the localized atrophic areas in the retina, small points of chorioretinitis may be present. Such areas are associated with retinovitreous adhesions corresponding to the scar. The mild focal chorioretinitis does not produce a dense proliferative scar and therefore leaves thin weakened areas that can be easily torn by traction of the adherent vitreous (Fig. 22). These strands may be extremely dense and capable of exerting great force in the form of traction at a localized point on the retina (Figures 23A, 23B, and 24).[35]

On the other hand, the dense chorioretinal scars formed following an exudative process rarely tear following traction from the vitreous strands, because the chorioretinal adhesions are so dense that they can withstand the pull.

The vitreous strands following severe chorioretinitis may be very dense and even cellular. The contracture of these cellular strands exerts great force and may cause a separation of the retina (Fig. 25A, 25B, and 26).

Secondary Holes.—There are different types of holes found in the retina in the presence of detachment. The usual horseshoe-shaped tear is probably formed by the presence of a retinovitreous adhesion in an eye where the vitreous has become shrunken and causes localized traction on this weakened area of the retina. Once the fluid has gained access to the subretinal space, the retina separates from its contact with the pigment epithelium and becomes elevated. The fluid in the subretinal space exerts further pressure on the retina and increases the area of detachment.

If this subretinal fluid migrates from above to the lower portion of the fundus, it may cause an elevation below. Such an

Fig. 25B.—A photograph of the same eye as shown in Figure 24, but both callottes have been removed to show the dense character of the strands.

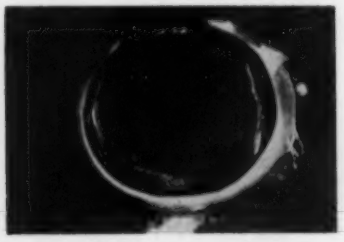
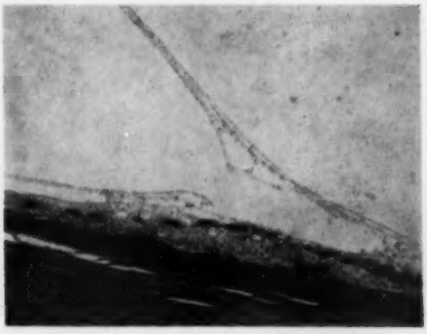


Fig. 26.—Microscopic slide of Figure 25B, which shows the cellular character of the dense vitreous strands.



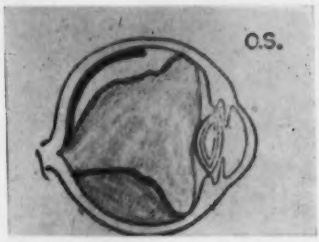


Fig. 27.—A diagram showing a hole in the retina above, with a large dependent detachment below.

elevation may be bullous, and there may be no holes in the lower portion of the retina (Fig. 27). On the other hand, one frequently sees one or more small punched-out dehiscences in the elevation. Such secondary

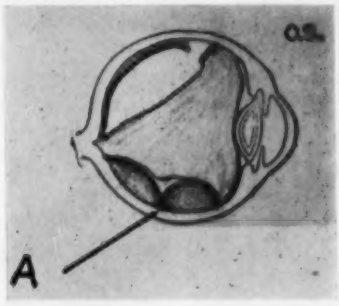
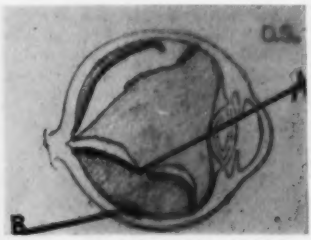


Fig. 28.—A diagram showing a hole in the retina above, with a dependent detachment below. The chorioretinal adhesion is a point where a potential secondary hole in the retina may form (*A*).

holes can be caused by the presence of small localized areas of chorioretinitis existing prior to the detachment (Fig. 28). When the fluid migrates to the lower portion of

Fig. 29.—A diagram showing a condition similar to that in Figure 28, but sufficient force has been exerted on the retina to cause a secondary hole to form (*A*) at the location of the chorioretinitis (*B*).



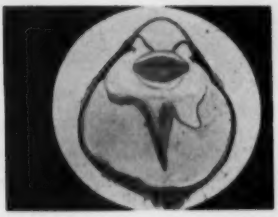


Fig. 30.—A photomicrograph of the eye of a 44-year-old woman who developed a detachment of the retina following diabetic retinopathy. The detachment was of long standing, and secondary glaucoma developed. A section of the globe shows a complete detachment of the retina.

the globe, sufficient force is exerted on the localized adhesions that either a hole is formed or the small areas of chorioretinitis are broken (Fig. 29). In this case, traction from within is not responsible for the pres-

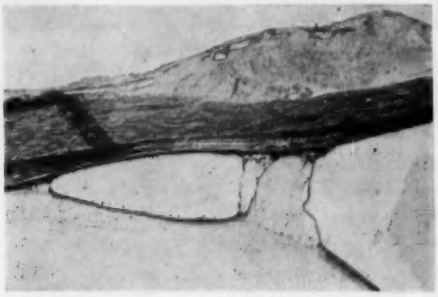
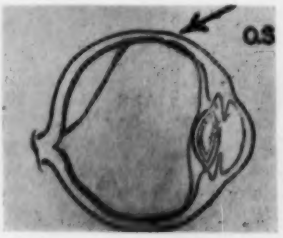


Fig. 31.—High-power photomicrograph of Area *A* in Figure 30, showing an area of chorioretinitis that has been under traction from the detached retina, causing thinning of the retinal elements. Further traction can easily cause a hole to form by a rupture of the thinned retina.

ence of the retinal holes. The force forming the secondary holes is exerted by the pushing effect of the subretinal fluid rather than by the traction from within (Figs. 30 and 31).

Fig. 32.—Diagram showing two small holes in the peripheral retina without detachment. The vitreous cushions the retina and exerts no traction on the lips of the hole.



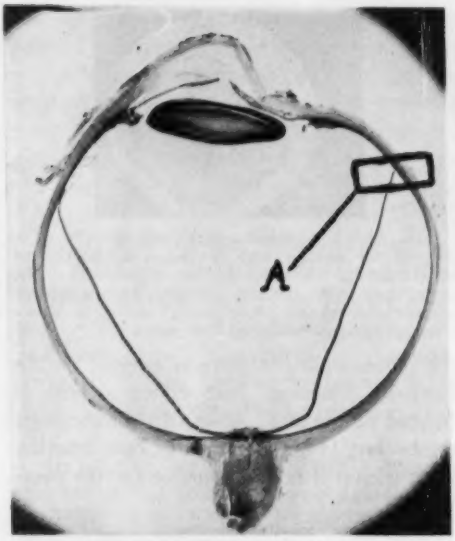


Fig. 33.—A photomicrograph of an eye taken from a 15-year-old girl who had an abscess of the cornea. There was no clinical evidence of detachment. The apparent detachment shown in the section is an artefact due to sectioning.

Peripheral Cysts.—In recent years, with the improved methods of examining the peripheral fundus, many small holes have been described in the absence of detachment

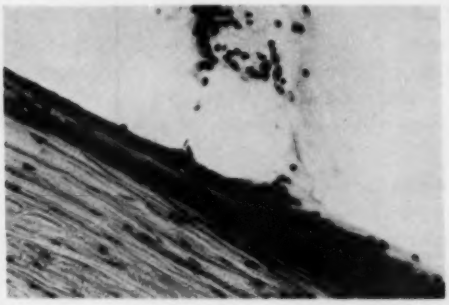


Fig. 34.—A high magnification of the peripheral retina in Area *A* from Figure 33. There is a small cyst at the ora serrata which involves all layers of the retina.

of the retina. These holes may be the result of small cysts in the periphery. The holes may remain unchanged without ever causing a detachment so long as the vitreous cushions this area (Fig. 32). The small peripheral cysts of the retina have often been blamed for detachment of the retina. But with a better understanding of the changes found in the vitreous clinically and macroscopically, as well as microscopically, one can conclude that such cystic changes are not the major cause of detachment (Figs. 33, 34, and 35).

Fig. 2.—A picture of a freshly enucleated normal eye taken from a young person with a neoplasm of the orbit. The vitreous is crystal-clear and fills the vitreous cavity.

Fig. 3.—A picture of a normal eye removed from a middle-aged person with an orbital neoplasm. The eye and orbital contents were fixed in Gonzalez' solution. The vitreous is clear and shows no evidence of shrinkage.

Fig. 4.—A picture of a normal eye removed from a patient in his early 50's. There was no history of eye injury or disease. The vitreous is clear and fills the vitreous cavity.

Fig. 6.—A picture of a normal eyeball removed because of an orbital tumor. The expansion of the tumor has caused a compression of the globe without obvious changes in the normal transparency of the vitreous.

Fig. 7.—A picture of an eye which had sustained injury from a perforating foreign body. The course of the foreign body is made clear by the condensation of vitreous in the form of fine striae.

Fig. 10.—A picture of an eye removed after iridocyclitis and secondary glaucoma. The section shows a posterior detachment and shrinkage of vitreous, but the hyaloid is still in contact with the optic nerve.

Fig. 12.—Picture of an eye from a 65-year-old man. In childhood a blow to the eye resulted in the loss of vision. Glaucoma developed two years prior to enucleation. A section of the globe reveals complete posterior detachment of the vitreous (*A*). The hyaloid is no longer attached to the optic nerve.

Fig. 13.—Picture of an eye removed from a 60-year-old man with a history of uveitis many years previously. Secondary glaucoma developed, with subsequent loss of vision. A section of the globe shows a complete posterior detachment of the vitreous (*A*), which is somewhat more advanced than that in the previous Figure.

Fig. 14.—Picture of an eye removed from a 79-year-old woman in whom acute glaucoma developed following eye examination. Tension was not controlled, and vision was lost. A section of the globe shows advanced shrinkage of the vitreous (*A*). The cushioning effect exerted by the vitreous is present only on the peripheral part of the retina (*B*).

Fig. 17.—A photograph showing the marked flattening of the sclera above the area where treatment was applied.

Figure 2

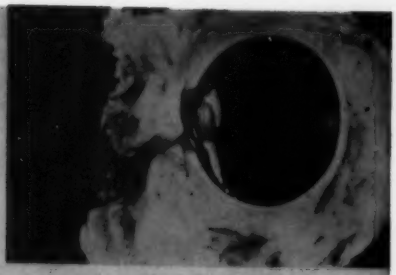


Figure 3

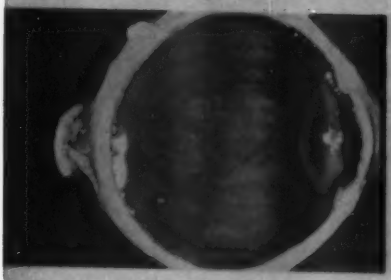


Figure 4

Figure 6

Figure 7

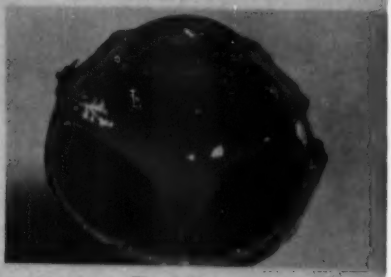


Figure 10

Figure 12

Figure 13

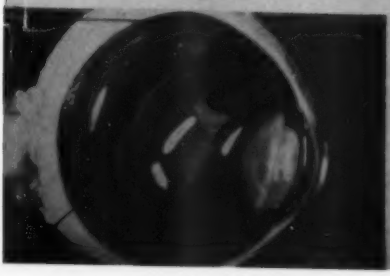


Figure 14

Figure 17

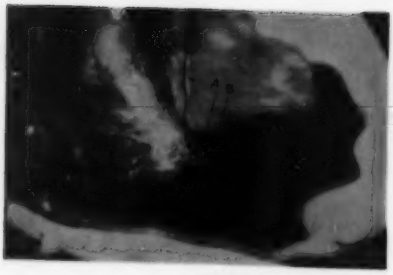


Figure 18

Figure 20

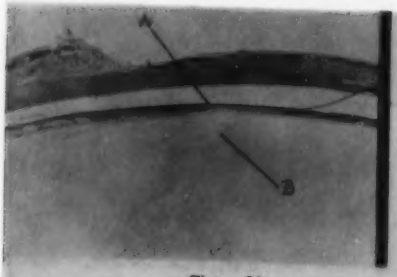


Figure 21

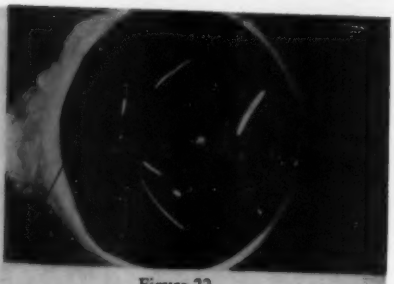


Figure 22

Figure 23A

Figure 23B

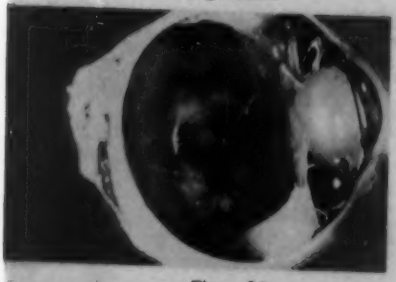


Figure 24

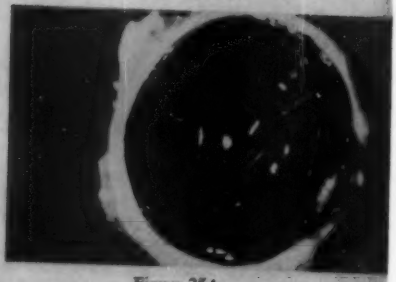


Figure 25A

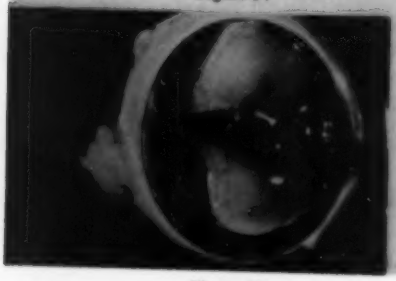


Figure 39

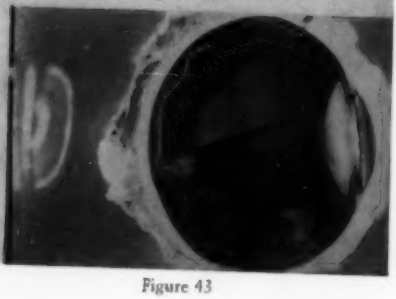


Figure 43

Fig. 35.—Serial sections of the cyst shown in the previous illustration reveal an actual hole at one point. There was an existing hole in the retina, but the vitreous cushioned this area and exerted no traction in order to cause a detachment.

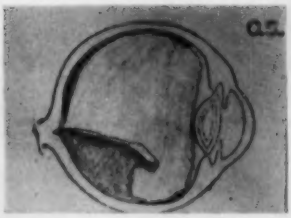


Fig. 36.—A diagram showing the vitreous protruding through a disinsertion and partially filling the subretinal space.

Disinsertion.—The mechanism of disinsertion is probably different from that of all other types of retinal tears or holes. A disinsertion frequently occurs following direct trauma to a normal eye. The retina tears from its attachment at the region of the ora serrata. As the hole is made, formed vitreous protrudes into the subretinal space through the large tear (Figs. 36 and 37). Since the tear may be plugged with vitreous, fluid does not migrate to the subretinal space. Therefore, the detachment may remain unchanged over a long period. On the other hand, the retina is separated by formed vitreous and may not respond to the usual diathermy barrage. It is usually necessary to apply diathermy applications in the area behind the vitreous in order to wall off the elevated region.

Vitreous Hemorrhage.—Associated with age and disease, vitreous hemorrhage may present itself as a part of a syndrome. In cases in which hemorrhage takes place and makes its way into normal vitreous, the blood remains dark and in dense strands, causing a prolonged decrease in vision. Ab-

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Fig. 18.—The interior of the eye, showing the shrunken vitreous adherent to the lip of the tear. The faint white spots surrounding the tear represent the diathermy barrage.

Fig. 20.—High-power photomicrograph depicting the retinal tear; beneath the retina is the choroidal hemorrhage. The tag of the retina is attached to the vitreous, as is represented by the faint-staining strands extending from the tag of the retina (*A*). Note that the retina is firmly reattached in the area of the hole.

Fig. 21.—A photomicrograph showing a localized area of retinal atrophy (*A*) with retinovitreous adhesions (*B*). Traction by the shrunken vitreous may produce a tear in the weakened retina.

Fig. 22.—A photograph of an eye taken from a 60-year-old man with history of repeated attacks of iridocyclitis associated with vitreous hemorrhage. Secondary glaucoma developed. A section of the globe shows numerous atrophic areas of the retina and focal chorioretinitis. The retinovitreous adhesions (*A*) could exert sufficient traction to tear the retina and cause detachment.

Fig. 23A.—A photograph of an eye taken from a 38-year-old man. A loss of vision developed following a blow to the eye. Glaucoma developed two years before enucleation. A section of the globe shows dense vitreous strands capable of exerting traction with great force.

Fig. 23B.—Callotte from specimen shown in Figure 23A, demonstrating scattered atrophic areas which probably represent inactive chorioretinitis. Note the vitreous adhesions to these scars.

Fig. 24.—A photograph of the eye of a 26-year-old man who developed detachment of the retina following trauma. Subsequent to operation there were repeated attacks of iridocyclitis and secondary glaucoma developed. A section of the globe shows extensive chorioretinitis with a shrinkage of the vitreous and fine vitreous strands adherent to the region of the scar.

Fig. 25A.—A photograph of an eye taken from a 47-year-old man who had repeated attacks of iridocyclitis. He later developed glaucoma. A section of the globe shows dense vitreous strands in the form of membranes which are firmly attached to the areas of chorioretinitis.

Fig. 39.—A photograph of a globe taken from a 66-year-old woman, with diabetes of long standing, who had a history of repeated vitreous hemorrhages. A section of the globe shows blood in the normal vitreous.

Fig. 43.—A photograph showing a detachment of the retina in the presence of a malignant melanoma of the choroid. Note that the subretinal fluid has coagulated following fixation of the globe.

Fig. 37.—A photomicrograph of an eye with a history of a bullous detachment following a disinsertion. The microscopic section shows the peripheral retina and disinsertion. The vitreous (*A*) extended through the disinsertion into the subretinal space when the globe was opened, but when the specimen was handled, the vitreous withdrew from the disinsertion. However, a small amount of vitreous is present in the retinal tear.

sorption of such blood may take months or even years (Figs. 38 and 39).

It is not unusual to see a patient with a recent vitreous hemorrhage that clears within 24 to 48 hours. This hemorrhage probably takes place in the retrovitreous space. Such an eye probably has a detachment of the vitreous with shrinkage, and the blood escapes into the area containing fluid behind the vitreous. Blood in this fluid medium settles rapidly, as blood in the anterior chamber quickly forms a hyphema (Figs. 40 and 41). A rapid return of vision may be experienced.

Such a mechanism is often seen prior to the formation of detachment of the retina. A small rent in the retina may tear a blood vessel and cause blood to fill the subvitreous space and obscure the findings. After the blood has absorbed or settled, one

Fig. 38.—A diagram showing hemorrhage into the normal vitreous. Blood in the gel may remain unchanged for months.

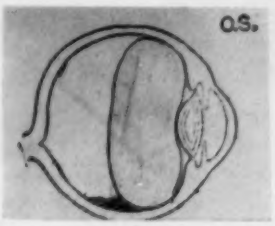


Fig. 40.—A diagram showing blood in the subvitreous space. The blood has settled into the dependent part of the globe. A gross specimen was observed, but photography was not possible, because the blood escaped with the subvitreous fluid at the time the globe was opened.

is able to find a tear in the retina and a small localized detachment.[36]

Subretinal Fluid.—Depending on the nature of the disease process, subretinal fluid has different characteristics. If there is a

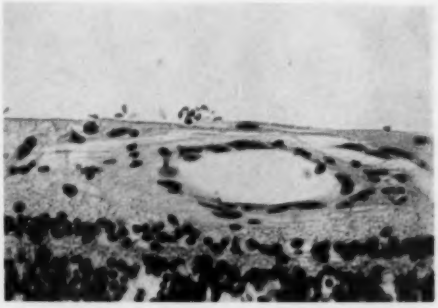
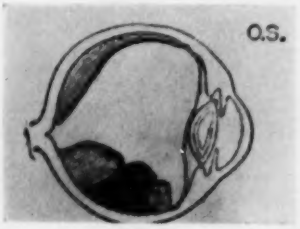


Fig. 41.—A microscopic section that shows hemorrhage on the surface of the retina following a subvitreous hemorrhage, as described in Figure 40.

serous detachment of the retina with a hole, the subretinal fluid remains liquid and does not coagulate on fixation. On the other hand, in the presence of a choroidal tumor

Fig. 42.—A diagram showing a detachment of the retina associated with a melanoma of the choroid. The subretinal fluid has coagulated on fixation.



with a secondary detachment of the retina where no hole exists the subretinal fluid is high in protein and quickly coagulates on fixation (Figs. 42 and 43). Such fluid gives a 4+ Pandy reaction, indicating an increased amount of protein. The same coagulability of the subretinal fluid is seen in inflammatory conditions causing a detachment—for example, Haroda's disease, toxemia of pregnancy, and localized chorioretinitis. Such definite differences in the subretinal fluid could very easily be a help in establishing the diagnosis in some individual instances.

Conclusion

Vitreous changes fall into definite patterns that may be confirmed by clinical, gross, and microscopic findings. Many of previously described artefacts are actually real changes in the vitreous. The vitreous plays an important part in health and disease of the eye. The mechanism of detachment of the retina is more clearly understood with our increased knowledge of the changes in the vitreous.

635 W. 165th St. (*32*).

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Coats' Disease

GEORGE N. WISE, M.D., New York

Michaelson [1] showed that embryonic retinal capillaries developed entirely from veins and stated that the retinal capillaries and veins should be considered one vascular unit. He proposed that all retinal vascular development occurred in response to some unknown tissue factor present in areas of relative retinal anoxia. As the capillary bed developed, nearby arteries with their higher oxygen environment had an inhibitory influence on the production of this unknown tissue factor and thus an inhibitory influence on capillary extension in their vicinity. At term retinal vascularization became complete; a state of equilibrium was reached, and further vascular formation ceased. Finally, Michaelson stated that the capacity of veins and capillaries to form new vessels did not disappear at birth but simply became dormant.

In a previous article [2] it was proposed that some degree of capillary or vein obstruction in the fully developed retina initiated the reawakening of Michaelson's dormant embryologic mechanism. With sufficient obstruction of any part of the venous vascular unit (capillaries or veins), circulatory stagnation and a state of relative retinal anoxia beyond the obstruction developed. Under these conditions, Michaelson's vasostimulating factor, normally absent in the mature retina, reappeared. In embryologic vascular development a preordained normal gradient of this factor insured an orderly development of the retinal vascular tree. In venous obstruction, depending on its degree, etiology, site and ramifications, a patchy distribution of this factor in varying concentrations called forth a disordered neovascularization and aneurysm formation almost totally from the regional veins and capillaries. Evidence was also presented [2] that so-called retinal microaneurysms were actually aborted neovascular buds arising as a result of this same neovascular-stimulating factor.

With use of these principles, a new explanation of the pathologic sequence in Coats' disease and several related conditions was suggested.

The literature will first be analytically reviewed. Each condition will then be explained in a new way, showing these various interrelations.

Coats [3-5] described under the title of retinitis hemorrhagica externa a pathologic condition occurring mainly in the young. He divided these into three groups: (1) cases without marked vascular changes, (2) cases with marked vascular changes, and (3) cases with arteriovenous communications.

Group 3 has subsequently been placed in a category of its own. It is now known as von Hippel's angiomatosis retina in its purely retinal form [6] or as Von Hippel-Lindau disease when the central nervous system is also involved.

Coats' original descriptions have been little changed until recently. He reported this disease of the young as usually involving only one eye. The general health and physical examination were normal. Those cases without vascular changes were commonly nonprogressive; those with such changes usually progressed.

The disease had a long protracted clinical course with remissions and exacerbations. Massive yellowish or white deep retinal exudation appeared first. It sometimes started posteriorly with tongues reaching out to the periphery or, at other times, started

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From the Department of Ophthalmology, New York University Post-Graduate Medical School.

peripherally in the vicinity of small venous radicles. While most of the exudation was deep to retinal vessels, where heavy, it occasionally reached up to cuff or cover them. The retina was extensively infiltrated and slightly elevated, or more localized exudation highly elevated it, at times to 10 or 12 D. Deep hemorrhages were almost always present and gave a variety of fundus colors. Fresh exudative patches occurred suddenly in new areas; older zones underwent cholesterin degeneration and absorption. As the disease aged, pigment proliferation became more prominent.

Vascular changes, when present, showed tremendous variation. Minimal changes consisted of vascular engorgement over exudative areas, increased arterial reflex, and peripheral vascular dilatation with occasional white sheathing. In other cases, vascular pathology seemed primary. In these, vessels near the disc were nearly normal while most change occurred in third- or fourth-division veins. Fusiform or pearl-like dilatations, ectasias, aneurysms, tortuosities, glomerular forms, anastomoses between abnormal vessels, and obstructions were all common. Such vascular changes were sometimes limited to a small area. Hemorrhages occurred in areas of most vascular pathology. Retinitis proliferans following vitreous hemorrhage was occasionally noted.

Later, retinal separation from the exudative border to the periphery was common. Final complications included iritis, cataract, hypotony, or secondary glaucoma with classic rubeosis iridis and ectropian uveae. Coats also noted occasional circinate figures about prominent posterior exudative masses.

One case [4] followed for 16 years exemplified the slowly progressive venous nature of this disease. The veins were involved early with all of the progressive changes enumerated above, while the arteries were always clinically normal.

Coats concluded that peripheral capillaries were first involved, with changes too subtle for clinical detection. He saw new patches of exudate where the vessels had repeatedly been found normal and stated that ophthalmoscopically recognizable vascular changes were not a necessary precursor of the disease.

In the original microscopic descriptions [3,5] a local, or flat and diffuse, mass of subretinal connective tissue was considered pathognomonic. Early, this tissue was loose and cellular; later it was less cellular and vascular but much thicker. Hemorrhages, leukocytes, and fibrin in the cystic edematous retina and loose subretinal tissue were usual. Outer retinal elements were partially destroyed or missing, while inner retinal layers were often very well preserved. In early stages the subretinal fibrous mass was always adherent to the retina. In later stages it was sometimes also adherent to the choroid. Bruchs' membrane and the choroid were usually normal. Some cases showing marked chorioretinal adhesion also demonstrated choriocapillary dilatation and a more marked vascularity of the subretinal fibrosis. In these few cases Coats believed the blood supply was partially derived from the choroid.

Later, scattered pigment proliferation, giant cells, and collections of ghost cells were common. The most involved retinal areas were thickened and often folded.

Finally, walled-off cystic spaces containing swollen leukocytes, broken-down hemorrhages, cholesterin crystals, pigment, and necrotic debris were seen subretinally. Calcification and bone formation were very late.

Coats also noted an occasional thin layer of fibrosis on the retinal surface, especially over an exudative mound. This will be referred to later.

Vascular changes, though sometimes absent or minimal, were usually marked. Hyalinized arterial walls, periarteritis, and occasional arterial obliterations were seen. By far, the most pathology occurred in veins. The latter showed massive dilatations with relatively normal walls, periphlebitis, narrowings, irregular knots and kinks, endothelial proliferation, and blockage by hemo-

genous coagulum. Intraretinal new vessels and especially neovascularization in the normally avascular outer retinal layers and subretinal connective tissue were regularly found. At times marked vascular changes were found only at the major lesion and in that retinal sector peripheral to it. Obstruction of a large venous trunk at the lesion could well account for this, in my opinion. Although serial cross sections were not made, Coats stated that there was neither clinical nor pathologic evidence of complete obstruction of the central vessels.

Subretinal fibrosis near the retina was more delicate, cellular, and vascular.[3] That farther from the retina was denser, more sparing in cells, and less vascular. Note how comparable this is to early and older retinitis proliferans. In one case (Fig. 1) he noted a vascular tuft, originating from the deep retinal capillary bed and projecting with its fibroblastic mantle through the external limiting membrane. Though going in the opposite direction, the complete similarity of this new vessel to those seen in early retinitis proliferans first suggested the concept offered in this report.

Coats [3] believed that hemorrhage from the deep capillary bed initiated this disease. Intraretinal blood then broke through subretinally causing detachment. Fibrotic and vascular organization of the subretinal hemorrhage completed the picture. He commented on the similarity of late complications in exudative retinitis and central vein thrombosis. And, finally, he called attention to the similarity of this process and retinitis proliferans, both of which he observed simultaneously in a few instances.

Leber [7-9] differed with Coats and described what he considered an entity—multiple miliary aneurysms with retinal degeneration. His cases all occurred in young males and showed clinically small or wide-spread groups of microaneurysms, mainly about the posterior pole and sometimes centered on the macula. The aneurysmal cluster was often surrounded by a girdle or broken arc of deep white exudates. Occasionally, in more exudative areas, the

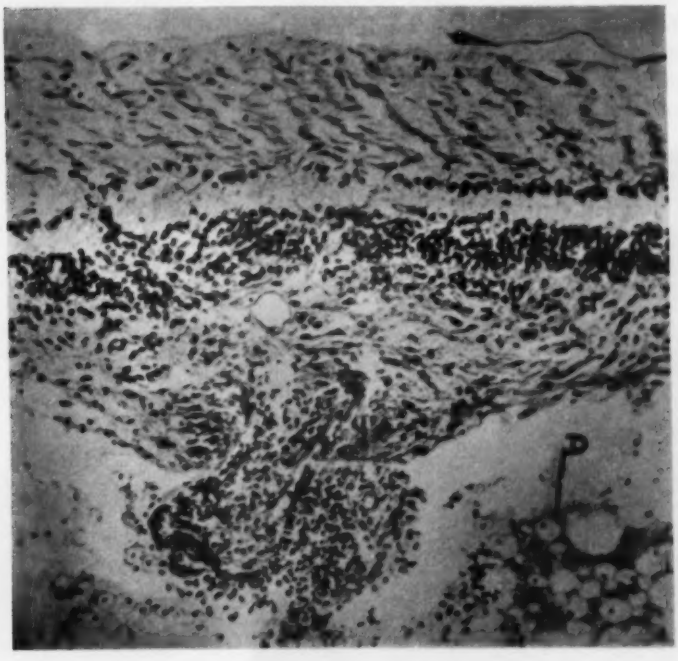

Fig. 1.—Reproduction of Coats' original illustration from his first case. Note the fibrovascular proliferation subretinally from a dilated capillary in the deep retinal vascular bed. This was in an area detached by massive subretinal exudation. Note the similarity of this to the early fibrovascular proliferation in human retrolental fibroplasia, except for the fact that the latter grows from the superficial retinal vascular bed toward the vitreous. (Reproduced with permission from Coats,[3] *Royal London Ophthalmic Hospital Reports*, J. & A. Churchill, Ltd.)

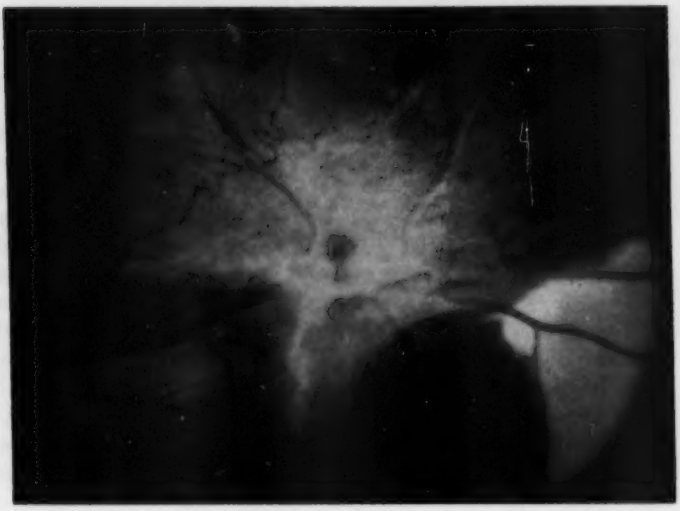

Fig. 2.—Man aged 24, Coats' disease O. S. Normal O. D. Note the massive fibrotic intravitreous proliferans from the obstructed superior temporal vein and the absence of vitreous proliferation in the area of massive exudation to the right. When the retina is against the choroid, proliferation is toward the vitreous.

vessels were covered. Leber stressed the arterial origin of most aneurysms, but he noted their definite occurrence on veins and probable origin from capillaries. Some aneurysms were filled with blood; others were white and obliterated. Their feeding vessels were often tortuous and narrowed; had thickened walls and abnormal communications and collaterals, or were obliterated. Most aneurysms occurred within the exudative ring; less frequently, in the retina beyond. In severe cases with widespread infiltration aneurysms were prone to appear overlying exudative areas. Some of the latter cases showed retinal detachment and retinitis proliferans. Uninvolved retinal areas, large vessels, and discs were normal.

While occasional small hemorrhages were seen among aneurysms, severe hemorrhages were so rare that Leber stated they played no fundamental part in the disease.

The similarity of this condition and Fuchs' circinate retinitis was noted by Leber. An extensive review,[10] to be pub-

Fig. 3.—Same patient as in Figure 2. A peripheral area showing aneurysms and superficial proliferation in the depressed central area where the retina is adjacent to the choroid. This is not seen in the surrounding areas of massive exudation, where fibrovascular proliferation is subretinal.

Fig. 4.—Same patient as in Figure 2, showing another peripheral area similar to Figure 3.

lished soon, shows the clinical and microscopic similarity of both to circinate lesions in diabetes, venous obstruction, and senile disciform macular degeneration.

The microscopic findings in most of Leber's cases were the same as those reported by Coats. Indeed, Leber believed that his cases represented early examples of Coats' second group and that this group comprised an entity. Noting that primary and secondary vascular changes were difficult to assess, both he and Coats believed this to be primarily a vascular disease. The exudative phase they considered secondary.

In general, Leber probably saw earlier cases than Coats; his cases showed more aneurysm formation, were more likely to show circinate figures, were less severe, and had less exudation. While both had the same microscopic pathology, Leber's group demonstrated more new vessel formation in the inner retinal layers.

Fig. 5.—Same patient as in Figure 2, showing fibrotic proliferans from the disc superficially along dilated and obstructed inferior temporal vein. Note that this is intravitreous, over an area of undetached retina. Note also that it stops at the border of an exudative mound below, where fibrovascular proliferation is subretinal.

Fig. 6.—Man aged 25. Normal O. D. Coat's disease O. S. Peripheral retinal area showing groups of superficial aneurysms and vitrous proliferation in areas where retina is more adjacent to the choroid and on borders of exudative mounds. Where retina is detached by exudation, fibrovascular proliferation is mainly subretinal.

Coats believed that his cases were due to the organization of hemorrhage from diseased capillaries and veins. Leber insisted that his was primarily a toxic or embolic arterial disease, in which hemorrhage was of secondary importance. Coats placed the aneusysms on the venous side of the circulation; Leber, primarily on the arterial.

As a new pathologic sequence is to be proposed in this report, the first part of this controversy can be omitted. However, it seems wise to pause here and reconcile these two conflicting views on the primary site of aneurysmal origin. What factors support Coats' venous or capillary origin as against Leber's view?

1. Coats did not mention arterial aneurysms in any of his cases. Leber, while insisting that arterial aneurysms were predominant, actually described both venous and probable capillary aneurysms in his.

2. Kraus and Brückner's case[11] was claimed by both Coats and Leber as an example of each disease. Review of this

Fig. 7.—Man aged 79. Circinate macular retinopathy O. D. Coats' disease O. S. A peripheral area of massive exudation containing cholesterin crystals. These show archipelago-like character of exudate border.

Fig. 8.—Woman aged 56. Diagnosis: old Coats' disease O. D. Area below disc showing obstructed vein, fibrotic intravitreous proliferans in lower left-hand corner. Note marked secondary arterial change. This entire area previously showed massive exudation as in Figure 7.

fundus illustration surely indicates venous as well as arterial aneurysms.

3. Leber [7] cited only two personally observed cases in his original article. The first was a 25-year-old man with absolute glaucoma and widespread miliary aneurysms. A recent review [2] has demonstrated the preponderence of capillary and venous microaneurysms in this disease. His second case —that of a 20-year-old youth—he saw only in consultation. Leber was the first to admit that his conclusions were drawn from a small series of cases—these 2, and 11 from the literature. Furthermore, two of his illustrated cases, Figures 3 and 4,[8] appear to demonstrate predominantly venous aneurysms. Also, Oeller's case,[12] which Leber included in his group, appears to show, according to the illustration, mainly venous aneurysms. Finally, Leber in his writings on retinal aneurysms [8] was not always explicit as to their venous or arterial origin. He described Reimar's case of central vein thrombosis as having arterial aneurysms, and it

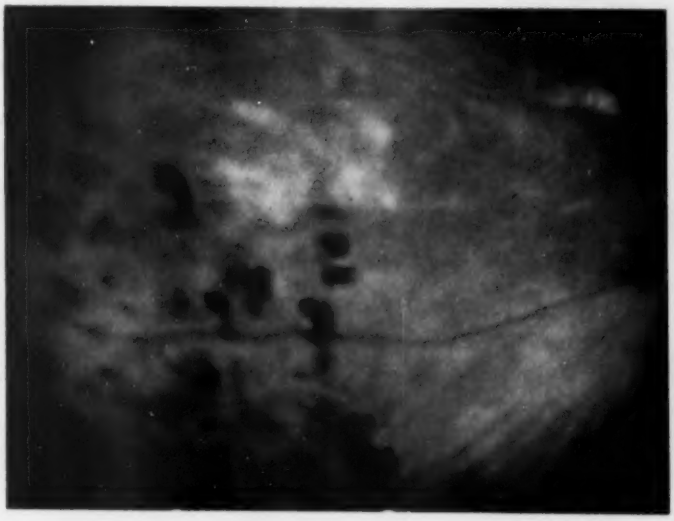

Fig. 9.—Same patient as in Figure 8. A peripheral area of previous exudation, showing the late pigment proliferation after exudate absorption. Note similarity of this to healed disseminated chorioretinitis.

was not clear on which side of the vascular system he placed the aneurysms of diabetic retinopathy and hemorrhagic glaucoma. As now seems clear, these are all predominantly capillary or venous in origin.[2]

4. Retinal microaneurysms have recently been much more extensively studied. Most are now thought to originate from capillaries and veins, in the various diseases wherein they occur.

5. Miyoshita and Nisyake's case of retinal degeneration with multiple miliary aneurysms [13] showed three aneurysms attached to veins, none on arteries, and others scattered without visible vascular connection. Microscopically, the pathology described by both Coats and Leber was present.

6. Kodilinye's case of miliary aneurysms with retinal degeneration [14] showed 11 aneurysms attached to veins and only 2 on arteries.

7. Gruber [15] did not specify an arterial or venous aneurysmal origin in his case of miliary aneurysmal retinitis (Leber). However, this case was strikingly similar to one reported by me.[16] The latter was considered a circinate macular lesion secondary to "silent" central vein obstruction which only subsequently became apparent. This would place the aneurysms of this case on the veins or capillaries rather than on the arteries.

8. Reese [17] considered the aneurysms of his retinal telangiectasis (Leber's disease) to be predominantly capillary or venous in origin. Indeed, several of his illustrated aneurysmal clusters were associated with venous changes usual in vein obstruction.

9. It is well to recall, at this point, the recent controversy over the arterial or venous origin of the diabetic microaneurysm. Clinically, it is often impossible to determine the vascular origin of cases in which it occurs. While arterial aneurysms undoubtedly do occur, and have been seen by me in a classic example of the disease described by Leber, most modern writings attest to their rarity as compared with capillary or venous microaneurysms. In my case just cited, three apparent arterial branches had multiple aneurysms like "berries on a stalk," as described by Leber. However, close examination with the slit lamp revealed that two of the three branches were vastly dilated arteriovenous communications and not arteries at all. Might not this too account for some of the discrepancy between Leber and Coats?

It seems reasonable to conclude that while Leber was correct in recognizing arterial aneurysms in this disease he erred in giving them preponderence over those of capillary or venous origin.

Morton [18] and de Schweinitz [19] both described cases clinically and microscopically [18] similar to those described by Coats. De Schweinitz noted two pertinent points: (1) the absence of retinal hemorrhage in one case; (2) the occurrence of the disease in a 60-year-old man. The latter was the first report of this juvenile and young adult disease occurring in the elderly.

Other reports have served to confirm Coats' original description.[20-32]

Lamb [33] described in detail six early and two late cases of exudative retinitis. He believed an albuminous, edematous fluid derived from retinal vessels first infiltrated the retina itself. This led to subretinal exudation and detachment. Retinal and subretinal connective tissue proliferation was a later phenomenon. Lamb agreed that the choroid took no part in the early phases and thought, as did Leber, that organization of hemorrhage was unimportant in the pathologic sequence of this disease.

Three of his early cases showed a delicate preretinal connective tissue, containing an occasional new vessel, over the summit of detached areas. At places this tissue extended as a thin membrane into the vitreous. Both late cases showed a greater degree of this same phenomenon. Lamb's major contribution was in noting that this delicate neovascular connective tissue was much more profuse just in front of the detachment at the ora and in the valleys between detached mounds. He said: "Where the

retina is less swollen, the internal layers are more involved than the external layers of the retina." In other words, where the retina was near the choroid, both neovascularization and connective tissue were found in the inner retinal layers and preretinally. Where the retina was detached and away from the choroid, only a delicate layer of neovascular fibrosis was preretinal, while the major fibrovascular proliferation was deep retinal or subretinal. The tremendous significance of this observation will be discussed subsequently.

Reese [17] made the most recent contribution to Coats' disease when he demonstrated, with periodic acid stain, a thickening of the vascular basement membrane sufficient, he thought, to occlude some vascular lumen. He considered this the primary lesion in Coats' disease, leading to vascular occlusions.

Reese substantiated Coats in noting more venous than arterial vascular lesions. He also confirmed Lamb in clinically noting more angiomatous changes in flat retinal areas. Opaque retinal areas, he thought, masked such changes.

Finally, Reese observed that two of his cases of Leber's disease—called by him retinal telangiectasis—progressed to Coats' disease.

Returning to the previously mentioned illustration of Coats' (Fig. 1), which first suggested a new explanation of this disease, one may see a neovascular capillary originating from the deep retinal capillary bed and growing toward the subretinal area. Its extremity is convoluted, resembling the neovascular glomerular tuft so frequently mentioned in the early retinitis proliferans of diabetes, retrolental fibroplasia, venous thrombosis, and Eales' disease.[2] In the latter the neovascular tufts project internally; in Coats' illustration it projects externally. Why, then, in Coats' disease did neovascular growth proceed in this "wrong" direction?

A New Concept of Coats' Disease and Related Conditions

In early retinitis proliferans the retina contacts the choroid and outer retinal layers are satisfactorily oxygenated by diffusion from the adjacent choriocapillaris. Following capillary and venous obstruction the circulation of the inner retinal layers becomes stagnated. With sufficient stagnation, these inner retinal layers become relatively anoxic. In such inner retinal layers of hypoxia, equilibrium is disturbed; Michaelson's dormant mechanism is awakened, and his unknown vasoproliferative factor develops locally. In response to this, new blood vessels with their fibroblastic scaffolding grow primarily from veins and capillaries in these inner hypoxic layers and overflow into the vitreous. Aborted neovascular buds remain as aneurysms intraretinally.[2]

In Coats' disease, early massive subretinal exudation (with or without hemorrhage) and subretinal masses of fatty granular cells mechanically detach the retina and block the outer retinal layers from their normal source of oxygen—the no-longer-adjacent choriocapillaris. If no venous or capillary obstruction ensues, the normally functioning retinal circulation insures adequate oxygenation of outer retinal layers as in bullous retinal detachment. No retinal areas become sufficiently anoxic, and equilibrium is undisturbed; no vasoproliferative factor develops, and aneurysms and new vessels fail to develop. Such is the course in Coats' Group 1 and Leber's purely exudative retinitis.[9,34,35]

With the onset of retinal capillary and venous obstruction in these latter circumstances, the oxygen status described above in retinitis proliferans no longer obtains. Inner retinal layers become relatively anoxic as before, but outer retinal layers, now utterly dependent on the complete integrity of the retinal circulation, become much more severely hypoxic. Under such circumstances, vasoformative factor develops in all retinal layers but is much more concentrated in outer retinal zones. In response to this,

neovascular fibrosis proceeds predominantly toward outer retinal layers and overflows into subretinal areas. Such is the course in Coats' Group 2.

What evidence further supports this thesis?

1. Von Hippel [6] described in his second case just such a glomerular convolute of capillaries as was illustrated by Coats. These originated from retinal vessels in an area where obstructed vessels had the character of small veins. The capillary tuft appeared in rudimentary outer retinal layers. In his first case, he found massive changes in outer retinal layers only where the retina was detached. This would be expected, for elsewhere the juxtaposition of retinal and choroid, with no intervening block, would insure that outer retinal layers would have adequate oxygen from the choriocapillaries. In such undetached areas, vasoformative factor would be more potent in the superficial retina and vasoproliferation would therefore be more obvious in these inner retinal layers.

2. Coats,[3-5] von Hippel,[28] Thomsen,[29] and Lamb [33] all found delicate preretinal fibrosis and occasional new vessels over the surface of detached areas. Lamb [33] drew particular attention to the marked increase of such preretinal tissue in undetached areas near the ora and deep in the clefts between detached mounds. Reese [17] noted more superficial angiomatous formation in undetached areas and believed that it was deep and hidden in the detached exudative mounds.

These findings are completely compatible with the proposed thesis. For, in detached and blocked zones, fibroblastic vasoproliferation should be toward the more hypoxic, outer retina. In undetached areas and in the clefts between exudative mounds, the subjacent choriocapillaris adequately supplies the outer retina and here vasoproliferation should therefore proceed toward the more hypoxic, inner retina.

3. In their studies on experimental retrolental fibroplasia, Ashton and Cook [36] noted an outward proliferation of new blood vessels to form a plexus under the retina in areas of detachment. In these same specimens there was an inward vasoproliferation forming intravitreous glomerular tufts deep in the grooves between detached mounds. The similarity of this to Lamb's previously stressed findings in Coats' disease is striking.

It is strongly suggested [2] that retinal capillaries and possibly small vein obstruction, secondary to wall adhesion after oxygen vaso-obliteration, play a fundamental part in the production of retrolental fibroplasia. Though it is clinically very different, a clear analogy of the sequence of pathology of this disease to that of venous thrombosis exists.[2]

The premature retina is still growing and is much more reactive than the mature retina. That oxygen will obliterate only the vessels of the immature retina attests to this fact. The growing, immature retina is undoubtedly more sensitive to oxygen deprivation. Therefore, simple detachment and separation of the outer retina from its choroidal oxygen supply is sufficient, in the presence of retinal capillary or vein obstruction, to make the outer retina more hypoxic. Thus occurs the outward vasoproliferation in detached areas of this experimental disease.

Because of the intense hypoxia in retrolental fibroplasia and therefore the high concentration of vasoformative factor, neovascular buds all progress to fully formed new vessels. Aneurysms have therefore rarely if ever been reported. One might anticipate a similarly high concentration of vasoformative factor in the outer retina of Coats' disease. If this is true, the finding of more inner retinal aneurysms and outer retinal new vessels in Coats' disease would also be explained.

4. Early retinitis proliferans in diabetes, retrolental fibroplasia, venous thrombosis, and Eales' disease has a delicate fibrosis and is very vascular. Later, fibrosis is heavy and vascularity is sparse. Similar findings have been noted in Coats' disease.

5. Evidence indicating that organization of hemorrhage plays no fundamental part in retinitis proliferans has been presented.[2] Leber's and Lamb's similar conclusions in Coats' disease seem most logical.

Conclusion

The thesis presented here seems to explain the variable clinical and microscopic findings in a variety of conditions—all considered by many as closely related but by others as individual entities.

1. Leber's exudative retinitis[9,34,35] is a chronic disease of youth characterized by massive subretinal serofibrinous exudation with retinal detachment. Outer retinal layers are mainly affected, and deep retinal or subretinal masses of lipid-containing bladder cells are characteristic. Hemorrhage plays a minor role, and retinal vessels are unaffected. No new vessel formation or subretinal fibrosis occurs. The explanation of this has been given earlier.

2. A clinical and microscopic description of Leber's multiple miliary aneurysms with retinal degeneration has been given. This disease is characterized by multiple zones of retinal hypoxia secondary to local capillary or venous obstruction. It is more spotty and milder than Coats' disease and would be to the latter as disseminated is to diffuse chorioretinitis. Its early exudative phase is mild, allowing the retina to remain more nearly adjacent to the choroid. Thus, in Leber's disease the hypoxia is greater in inner retinal layers. Aneurysms and sometimes fibroblastic vasoproliferation are therefore readily visible on the retinal surface, the latter especially at the centers of these hypoxic areas. When Leber's disease enters its more exudative and degenerative stage, the retina is more separated from the choroid by blocking exudation and fatty granular cells. Outer retinal layers then become more hypoxic and neovascular fibrosis proceeds subretinally. An early stage of Leber's disease, with widespread superficial aneurysms which suddenly became exudative, would explain the sporadic report of profuse aneurysm formation on the surface of exudative mounds. The explainable relation of Leber's disease to circinate retinopathy is the subject of another report.[10] Reese's[17] two cases of Leber's disease progressing to Coats' disease are thus understandable.

3. Reese's massive retinal fibrosis[37] clinically and microscopically closely simulated a localized mound of Coats' disease. One case had a circinate figure around the mound. Chorioretinal adhesion prevented any marked retinal detachment. Vascular changes and new vessels were present. All three cases showed retinal and subretinal fibrosis, fatty granular cells, cystic retinal degeneration, and destruction in all retinal layers, though more marked in the outer. The illustration of Case 2 strongly suggested the type of venous cuffing seen in retinal vein obstruction.

Here, the chorioretinal adhesion prevented much displacement of outer retina from its choroidal blood supply. Therefore, though hypoxia was still greater in the outer zones it was more intense than usual in the inner retina. Thus, neovascular fibrosis was present in all layers and more marked in the outer layer.

4. Coats' disease has been discussed.

5. The possible explanation for an occasional case of retrolental fibroplasia showing the microscopic findings of Coats' disease has also been given.

In this way, Coats' disease and an occasional case of retrolental fibroplasia might be considered external retinitis proliferans, while massive retinal fibrosis would represent an intermediate stage between this and the usual form of internal retinitis proliferans.

Dr. Albert Graemiger and Dr. Jaras Shegedyn aided in making the translations; Mr. Walter S. Lentschner did the photography, and Mrs. Joyce Rolls gave technical, library, and clerical aid.

550 1st Ave. (16).

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Case Reports

Blindness Secondary to Unusual Cyst of the Sphenoid Sinus

COLLIN S. MacCARTY, M.D.; JOHN C. LILLIE, M.D.; DAVID D. DALY, M.D.; ROBERT W. HOLLENHORST, M.D., and COLIN B. HOLMAN, M.D., Rochester, Minn.

Visual loss secondary to compression of the optic nerves and chiasm by meningiomas, pituitary tumors, Rathke's pouch tumors, epidermoids, chordomas, aneurysms, and secondary malignant processes in the area of the optic chiasm and nerves is encountered fairly often in an extensive neurosurgical practice. Generally, the diagnosis is apparent preoperatively. Roentgenograms of the skull disclose osteomas, "ballooning" of the sella turcica, suprasellar deposits of calcium, or secondary erosion of the sella turcica and clinoid processes. Examination of the visual fields in most instances reveals bitemporal hemianopsia of greater or lesser degree. Rarely should a diagnosis be made of malignant invasion of this area without microscopic identification of the lesion.

We wish to present an unusual case in which the situation appeared to be hopeless preoperatively but in which surgical relief was easily accomplished. We should like to emphasize the fact that this particular type of condition has rarely, if ever, been encountered previously. We believe that the technical surgical aspects of the case are worth recording in detail.

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Sections of Neurologic Surgery (Dr. MacCarty), Otolaryngology and Rhinology (Dr. Lillie), Neurology (Dr. Daly), Ophthalmology (Dr. Hollenhorst), and Roentgenology (Dr. Holman), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Report of Case

A 60-year-old registered nurse was admitted to the hospital and to the services of the Mayo Clinic on July 17, 1955, complaining of failing vision of five weeks' duration. Four months prior to her admission she had noted a dull headache. Hypertension (pressure of 190 systolic and 90 diastolic, in millimeters of mercury) had been diagnosed by her physician at home, and therapy with Rauwolfia was begun. The headaches had become progressively severe. Five weeks before her admission pain occurred in the left infraorbital region, and diplopia and blurred vision were detected in the left eye. The left eye became swollen shut, and within 24 hours it was blind. The swelling subsided, and the diplopia disappeared. Ten days before the admission of the patient, the vision in the right eye failed, so that the patient could not read a newspaper. Vision in this eye deteriorated so that at the time of admission the patient was almost completely blind.

When examined at the hospital this patient could count fingers with the right eye but could not read. The left eye was blind. Both pupils were dilated; the right, 4 mm., and the left, 6 mm. The right pupil reacted to light, but the left did not react to direct light. It did react consensually when light was thrown into the right eye. The left eye was slightly divergent and did not move well medially. Corneal sensation was intact. The fundi were essentially normal, and the optic disks were normal. Charting of the

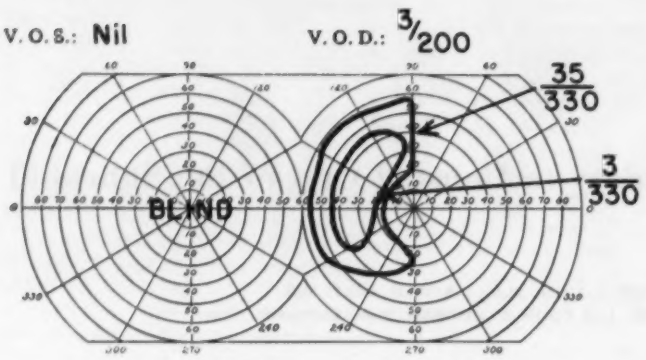


Fig. 1.—Visual fields on July 18, 1955.

perimetric fields disclosed a blind left eye and temporal anopsia with a central scotoma in the visual field of the right eye (Fig. 1).

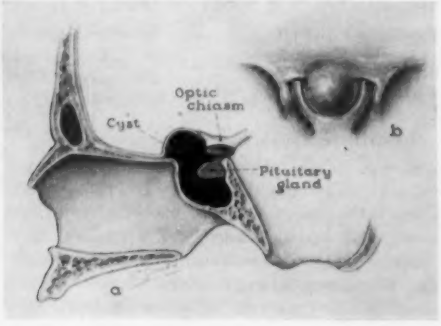
There was no physical evidence of pituitary insufficiency. The general examination revealed nothing of significance. Investigation of the ear, nose, and throat revealed the tympanic membranes to be scarred from previous infections. Hearing was normal. No tumor was visible in the nasopharynx.

Roentgenograms of the head revealed destruction of the sella turcica which appeared to be secondary to a malignant process or a chordoma, or possibly to a meningioma (Fig. 2). A roentgenogram of the thorax showed nothing abnormal. Results of urinalysis, the hemoglobin content, the erythrocyte count, and the leukocyte counts were normal.

Administration of a cortisone preparation was begun on July 19, 1955, in preparation for operation in the region of the hypothalamus and the pituitary gland. On July 20, 1955, right frontal craniotomy was performed. An intradural approach was utilized to expose the region of the optic nerves and chiasm. There was no evidence of increased intracranial pressure. It was seen that the superior aspect of the sphenoid bone had been completely eroded, so that the dura separated the sphenoid sinus from the optic nerves and inferior surface of the brain. The dura in this site was tense and appeared in the form of a blue-domed cyst (Fig. 3*a*) between the optic nerves, which it was compressing (Fig. 3*b*). A spinal-puncture needle was introduced into this cyst, and 10

Fig. 2.—Extensive decalcification of the body of the sphenoid bone, with sparing of the anterior and posterior clinoid processes. The ethmoidal and maxillary sinuses are normal.

Fig. 3.—(*a*) Sphenoid cyst, showing relationship of cyst to the surrounding structures. (*b*) Compression of optic nerves by the cyst.



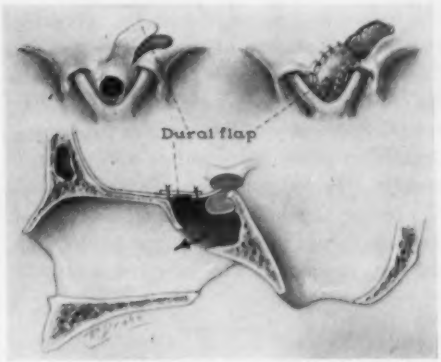


Fig. 4.—The surgical procedures done on July 20 to accomplish eradication of the sphenoid cyst are indicated. The intracranial evacuation of the cyst was accomplished by way of an incision between the optic nerves. This hole was repaired by reflecting a flap of dura from the wing of the sphenoid. The transnasal procedure done on Aug. 10 likewise is shown, indicating the method of drainage of the contents of the cyst into the nasopharynx.

cc. of yellow cloudy fluid was aspirated. This action immediately decompressed the optic mechanism and exposed both optic nerves, the chiasm and the pituitary gland. The pituitary fossa was composed of dural membrane without bony walls, as a result of continuation of the sphenoid cyst. An incision was made in the dura anterior to the chiasm, and the sphenoid was entered. The contents of the cyst were completely evacuated, and after considerable difficulty we were able to obtain a portion of the lining of the cyst, which consisted of squamous epithelium. There was no evidence of a malignant process. To repair the incision into the sphenoid sinus, it was necessary to reflect a flap of dura from the right sphenoid ridge and suture it over the defect (Fig. 4). This was accomplished with four absorbable surgical (gut) arterial sutures, and it effectively repaired the defect. The wound was closed in layers without drainage. The pathologic report was "inflammatory cyst partly lined by squamous epithelium."

The postoperative convalescence was normal. On Aug. 5, 1955, the ophthalmologic examination disclosed slight pallor of both optic disks. The left eye remained blind. Corrected visual acuity in the right eye was 20/60, and the reading vision on the A. M. A. reading card was 14/42. The visual field was contracted temporally, but a central scotoma was no longer demonstrable (Fig. 5).

On Aug. 10, 1955, a good-sized opening was made in the face of the right sphenoid sinus via a transnasal approach (Fig. 4). Yellow cystic fluid escaped when the sinus was first entered. Some mucous membrane was removed. The dura which comprised the roof of the sphenoid appeared to be intact.

After this procedure rhinorrhea did not develop. Headaches did not recur. Vision remained good in the right eye. On Jan. 28, 1957, the patient's ophthalmologist reported that the vision of the patient was 20/20 in her right eye, with the use of glasses. The left eye remained blind.

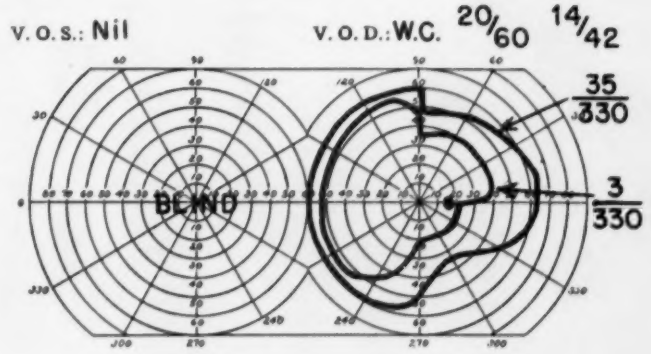


Fig. 5.—Visual fields on Aug. 5, 1955.

Results of culture of specimens of the cystic fluid removed by the intracranial route were reported as negative for fungi, Mycobacterium tuberculosis, the usual bacteria, and Brucella organisms.

Comment

The lesion in this case might be considered to be an unusual cyst of the hypophysial duct situated below the hypophysis, as reported by Dandy.[1] It appeared to the surgeon and pathologist, however, to be an inclusion cyst of the sinus without any gross resemblance to the usual Rathke's pouch cyst or epidermoid tumor. Neither the lining of the cyst nor the fluid contents resembled those found in these two conditions. There was no solid tumor associated with the cyst described in this report. The pituitary gland appeared grossly to be intact. This lesion actually seems to represent an inflammatory squamous cyst of the sphenoid sinus which presumably developed as a consequence of inflammatory closure of the sphenoid os. Gradual expansion of the cyst eroded the sphenoid sinus in the region of the sella turcica and compressed the optic nerves and chiasm, resulting in almost complete blindness. Identification and radical removal of the lesion was accomplished intracranially, and the compression of the optic nerves and chiasm was relieved. The approach into the sphenoid sinus was repaired and allowed to heal sufficiently well to prevent subsequent rhinorrhea when the sinus was opened transnasally. The latter procedure was necessary to prevent the sphenoid sinus from again becoming plugged, refilling, and again causing compression of the optic mechanism.

Summary

A patient who appeared to have an incurable lesion of the sphenoid sinus, with secondary blindness, is reported upon. A benign cyst of the sphenoid sinus was eradicated by transcranial and transnasal operation, and the recovery of vision was marked. It is presumed that the condition was thereby eliminated. The technical aspects and rationale of the operation are emphasized.

Mayo Clinic.

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A Temporary Lens for Aphakia

PAUL C. CRAIG, M.D., Reading, Pa.

For a number of years a special lens has been employed after operation for cataract. It gives fair vision to a number of aphakic patients. It can be used the day after operation, but ordinarily it is given at the first posthospitalization visit of the patient to his ophthalmic surgeon. This lens has an additional advantage in that it limits ocular rotation. It might therefore help forestall retinal separation and other postoperative complications.

Description of the Lens

The lens is 30 mm. in diameter and has a paper-thin edge. Its proximal curvature equals −6.00 D. sph, and its distal curvature equals +18.00 D. sph. Thus the effective refractive power of the lens is +12.00 D. sph. It fits readily on the outside of the patient's own glasses, which frequently have a base curve of +6.00 D. sph.

Use of the Lens

The lens is placed on the patient's old glasses and fastened with six short strips of ½ in. cellophane (Scotch) tape, leaving a central opening 15 to 20 mm. in diameter. The optical center of the lens is arranged in such a way that it is 2 mm. below the physical center of the spectacle cell.

With the use of this lens the patient can become accustomed to aphakic vision without a feeling that the final result has been reached. He is aware that this lens is temporary and preliminary and that future correction of his aphakia will be much more satisfactory.

Incidentally, when refracting for permanent correction it is well to compare the trial frame refraction with a refraction done over the temporary correction in the patient's own frame.

Needless to say, this lens will not be helpful to a patient with a functioning fellow eye. It is of value, however, for the one-eyed aphakic or the patient with advanced lenticular opacities or other pathology in his other eye.

Summary

A lens is described which gives some aphakic patients useful vision soon after operation.

232 N. 5th St.

Received for publication April 23, 1957.

Vision Chart for the Ophthalmoscope

EVERET H. WOOD, M.D., Madison, Wis.

Fig. 1.—The reduced chart, actual size.

Ophthalmologists are frequently called in consultation to see patients that are bedridden, and it is difficult to determine the extent of that patient's visual acuity unless some special equipment is carried along for the purpose. Since vision is the primary reason for eyes in the first place, it is essential in every eye examination that an estimation of the visual efficiency be made.

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From the Department of Ophthalmology, Jackson Clinic.

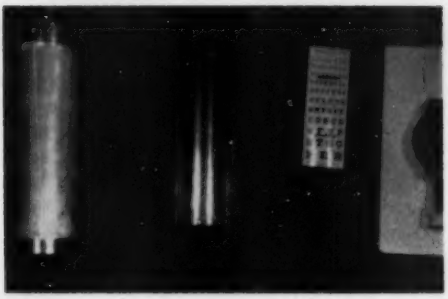

Fig. 2.—Component parts. Left to right, ophthalmoscope handle, transparent plastic sleeve, reduced chart, ophthalmoscope head.

In an attempt to provide a solution to the problem, the following simple device is offered. It consists of a reduced A. M. A. vision chart calculated to be read at 24 in., placed on the ophthalmoscope handle, and held in position by a transparent plastic sleeve. The chart then becomes a permanent part of the ophthalmoscope and provides an easily transported convenient method of determining vision.

Recording of the results of this test can be made by the same basic method as is used for vision at 20 ft. Since the chart is reduced to one-tenth the size of the standard Snellen chart, the recording can be expressed as 2/2 for standard vision, or equivalent to 20/20; 2/2.5, equivalent to 20/25,

Fig. 3.—Same as Figure 2, with chart in place within the sleeve.

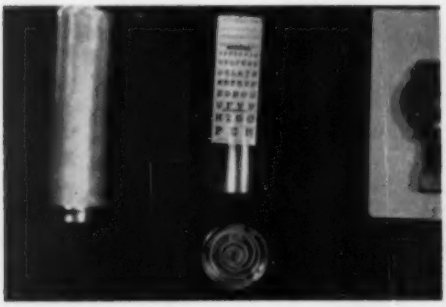

Fig. 4.—Ophthalmoscope handle with sleeve and chart in place.

and so on, in accordance with the usual method of recording vision. Notation that the reduced chart was used should be made. Presbyopic patients should have their presbyopic correction on, while younger patients can be tested both with and without correction.

It is recognized that the exactness of this test leaves something to be desired. Nevertheless, it does provide a much better and measurable method of recording vision and will serve as a substitute for what many ophthalmologists now use, namely, having the patient read or try to read some passage from a newspaper or magazine or no attempt at all to estimate vision on bedridden patients.

Welch, Allyn & Co. manufactured this device for me.

Jackson Clinic, 30 S. Henry St. (3).

Ophthalmological Reviews

Leptospiral Uveitis

G. E. ROWEN, M.D., Miles City, Mont.

Leptospirosis is a spirochetal systemic disease with protean clinical manifestations. In the early phase of the disease the organisms are blood-borne and are capable of lodging in any organ or organs, including the eye. Consequently, the multiplicity and and variation of signs and symptoms are determined by the system or systems involved. The most commonly known clinical entity related to this group of organisms is Weil's disease, caused by Leptospira icterohaemorrhagiae, which has a predilection for the liver. Although jaundice commonly occurs, it is not a necessary component and is merely a manifestation of gross liver involvement, which is not present in the majority of cases. The incidence of jaundice varies, and in one series of 81 patients no jaundice was reported.[1,2] However, it has been stated that there is no mortality unless jaundice is present.[3]

The disease has a world-wide distribution. The incidence of this disease is higher in Europe than in the United States, although no widespread surveys have been conducted in the United States, probably because the serological test can be done only in a few laboratories in the United States. It reaches a peak incidence in the late summer, about September. The age group most commonly involved is between 20 and 50, with a preponderance of males involved.[4]

Epidemiologically, the rat is the most important carrier and excretes the organism in large quantities in the urine.[5] More recently it has been found that dogs, horses, and cows may harbor the organism.[5-8] It is proved to have caused outbreaks of abortion storms in cattle in the U. S. A.,[27] and there is strong serologic proof that it causes periodic ophthalmia in horses.[10,25,26] It has been recovered from the conjunctival secretion of animals[9,10] and humans[10] as well as from muscle biopsy specimens.[9,11] Experimentally, it has been shown that the organisms enter the body through the conjunctival sac.[8] The organisms also are known to enter via mucous membranes and skin abrasions. In the Netherlands it is stated that the disease is contracted by persons just falling into the canals.[4] In some unpublished data there is evidence in support of direct invasion of the eye.[6] The incidence is higher in certain occupations than in the general population. These occupations involve contact with unpurified water and animals,[3,27] and included are dock workers, fishery workers, sewer workers, farmers, poultry producers, and slaughterhouse workers. However, a pet dog or cat may harbor the organism.

Apparently Leptospira organisms are an important cause of uveitis in Europe and this uveitis may be susceptible to specific therapy. However, this etiology has received little attention in American literature. This may be due to either a low incidence or lack of awareness of the potentialities of this organism by American investigators. It is the purpose of this report to review the salient features of the ocular manifestation of leptospirosis and to present the presently known data of its occurrence in this country.

From a complete review of the American literature it is apparent that the leptospiral organisms account for a number of cases of uveitis every year. However, the true inci-

Recorded for publication June 5, 1957.

Material collected during ophthalmology residency at University of Oregon Medical School.

dence of uveitis due to Leptospira cannot be determined from the papers reviewed in which the etiology of uveitis has been classified. A number of patients were studied at the University of Oregon Medical School to determine whether the leptospiral organisms were responsible for any of the cases of uveitis seen in the ophthalmologic clinic. Although the number is not statistically significant, they are herein reported. Twenty-five cases of all clinical types of uveitis were given agglutination tests for L. canicola, L. icterohaemorrhagiae, and L. pomona. Two different blood samples were studied two weeks apart, and all studies were negative. Nine of these patients had agglutination tests on the cerebrospinal fluid, with no positive titers. During this same period 25 patients with jaundice secondary to hepatitis were checked, and none of these had a positive titration. The serum of a sick dog was sent in during this time, and it was strongly postive to L. canicola. Twelve of the twenty-five uveitis patients had aqueous cultures for leptospiral organisms, with no growth recorded.

The reported incidence of iritis accompanying leptospiroses ranged from 3% to 55%.[3-5,12-14] The reported incidence of the iritis in Weil's disease varies according to the organism involved. In one survey L. canicola was found to cause 11.5% of cases, whereas L. pomona and L. grippotyphosa caused 5% and 32%, respectively.[13] Another reported 33% of cases with L. australis A, 14% with L. australis B, and 10% with L. icterohaemorrhagiae.[15] There is no correlation between the species and the incidence of iritis or the severity of the infection. The relationship to the presence of jaundice is undetermined. Of 29 cases reported, 19 were without jaundice and 10 were with jaundice.

Iritis may occur weeks or months after all signs and symptoms of the general disease have been absent. Subclinical uveitis has been reported in a systematic examination of patients recovering from the systemic disease.[30]

Symptoms

The onset of the uveitis is usually sudden. There is a ciliary flush, as in most cases of uveitis, which should not be confused with conjunctivitis, which commonly accompanies the disease. On biomicroscopy, pigmentation of Descemet's membrane has been reported.[30] A visible beam is almost always seen, accompanied by numerous cells. The keratic precipitates are described as fine- to medium-sized. White strands of fibrin appear in the anterior chamber, and a yellow pupillary membrane peculiar to this type of uveitis may occur.[14] Brown-gray nodules have been reported in the iris.[10] Posterior synechiae may or may not form. Vitreous haze is also reported occasionally.[13] The fundus is sometimes involved with a peripapillary edema. However, there is usually no retinal or posterior choroidal involvement.[12,13]

Diagnosis

In at least two different cases[13,16] the organisms have been cultured from the aqueous, and one of these almost amounts to a human experiment. A doctor, while working with the organisms, accidentally splashed a culture into his eye. Eleven days later the signs and symptoms of a systemic illness appeared. At this time, the organisms were cultured from his blood. Fifty-one days from the onset of the disease and thirty days after he had been symptom-free he had the onset of an iritis. The organisms were then cultured from the aqueous. Although the organisms were cultured from the eye at this time, no other systems were involved.

During the febrile state (first four to five days) organisms are found in the blood and may be seen by dark-field examination or cultured.[17] Positive dark fields have been found for three days after the fever has subsided. After this, there are agglutinins in the blood and the organisms may be cultured from the urine. If there are no agglutinins in the blood in 30 days, some other disease should be considered.[3] Agglutinins

have been found on the 105th day after the onset of the disease.[10] In those instances with central nervous system symptoms the organisms are frequently obtainable in the cerebrospinal fluid and agglutinins are also present.[8] These may be present in the cerebrospinal fluid five months after the onset of the illness.

The diagnosis can be made by finding blood agglutinins. An agglutinin titer of 1:300 or more is considered necessary to make the diagnosis.[12,19] This titer may remain high for several years.[20] Positive agglutinations have been recorded a number of times with titers varying from 1:30 to 1:32 for the aqueous.[14] At this same time the blood agglutinins may be 1:800.

In two different specimens of aqueous the cells were predominately lymphocytic in type.[10] There have been no histological reports of the eye in the literature reviewed.

Treatment

The treatment for the disease is not definitely established. For the iritis alone the usual method of cycloplegia and fever therapy seems to work.[12,16,19] No report of use of cortisone topically was found. In a series of 67 cases in Puetro Rico chloramphenicol, chlortetracycline (Aureomycin), penicillin, streptomycin, oxytetracycline (Terramycin), and cortisone were used in various combinations for the general disease, and the conclusion was that none of these helped. The best treatment is believed by some to be whole blood transfusions received from recovered patients.[21]

Course

The course is usually mild, with few sequelae.[13] Hypopyon and plastic iritis with relapses have been reported. Japanese authors are said to have observed severe eye complications.[13] There was no follow-up study done on any of the cases reported in the literature reviewed. Of 23 iritis cases reported only 1 case is reported with decreased visual acuity.[19]

Conclusion

Leptospiral organisms are responsible for a significant number of cases of uveitis annually in Europe. The incidence of this disease is unknown in the United States. This may be due to a lack of awareness of its existence by American ophthalmologists.

Medical Arts Bldg.

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Annual Reviews

Neuro-Ophthalmology

DONALD J. LYLE, M.D., Cincinnati

In my effort to select from the literature of the past 12 months neuro-ophthalmologic material, and arrange it for easier documentation, some unintentional omissions of pertinent subjects may have been made. Some literature, mostly foreign, antedating the period covered by this review, but not available for the previous review, is included. On the other hand, there may be some duplication as reviewers of other phases of ophthalmology have presented or will present some of the same material because of overlapping subjects. I have endeavored to present material when it provides a comprehensive review or thorough study and lucid presentation, especially if it is thought-provoking. Individual case reports, if they do not provide new concepts, have been omitted.

Papilledema

The study of the underlying causes producing choked disc is of perennial interest. Some believe the matter settled, but I for one am not quite sure that all of the answers are in. There are a number of conditions capable of disturbing the metabolism of the papilla, which, because of its water-binding proclivity, may swell to considerable amount. Not infrequently one is asked to give his opinion on the state of the papilla. He sees a disc with feathery outline and slight venous engorgement with one or two hemorrhages at the disc margin or in the adjacent retina. Elevation of the papilla is questionable. Is this beginning papilledema?

This topic is extremely well presented in Bregeat's [1] book, wherein he discusses the anatomy and physiology of the papilla and describes the types of papilledema, supported by clinical studies. Niedermeier [2] experimentally investigated the pathogenesis of papilledema, which he produced in animals by intradural injection. He concludes that papilledema develops as a local process, not as an extension of cerebral edema. François, Verriest, and Beheyt [3] discuss the diagnosis between papillitis and papilledema, stressing the value of visual fields in their differentiation.

Martelli [4] reviews the literature of Foster Kennedy syndrome and reports a case of vascular origin confirmed by angiography and craniotomy. Frezzotti [5] discusses the localizing value of Foster Kennedy syndrome and cites a case of the inverted syndrome. This article is succinctly discussed by Henderson.

False, or pseudo, choked disc is the subject of a paper by Marquart,[6] who describes the appearance of the disc in 18 cases, chiefly of refractive anomalies, drusen, and vascular lesions. To this, I believe, should be added persistent developmental remnants at the disc.

Merkulov [7] caused choked disc to disappear, by dehydration and promotion of absorption with use of Biochinol, in five cases of intracranial tumor proven at autopsy. Temporary reduction of brain swelling may aid in diagnosis and localization, but this procedure should be condemned as a means of treatment.

The Optic Nerve

In an article on the present status of optic atrophy Henderson [8] urges investigation of the cause, even though vision is irreparably

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lost, as the process, if allowed to remain, may damage other structures and jeopardize life. This admonition should be emphasized.

Ferreira [9] reviews the literature of optic atrophy and describes the differences between so-called primary and secondary types.

A syndrome found in hereditary infantile optic atrophy with dominant transmission is described by Kjer,[10] who studied 20 families, in which this condition affected 249 members.

Helmick [11] reports a case of tabetic optic atrophy and discusses treatment of this condition. He states, in brief, that heavy metals slow the process but do not prevent ultimate blindness. Malarial treatment may be of value. At present, penicillin, in large doses, is by far the best therapeutic agent. It should be administered early to prevent optic atrophy. Favre [12] presents a case of syphilitic perineuritis of the optic nerve, in which he emphasizes earlier and better diagnosis for curative treatment.

Two articles on optic neuritis during lactation appear in the current literature. One is by Nonenmacher,[13] who describes the symptoms in two patients; the other, by Pflieger,[14] who suggests endocrine disturbances and autointoxication as causative factors. No mention was made in either of these articles of tests to determine the calcium level or parathyroid function. I believe that these are the essential causes of this condition.

Trauma to the optic nerve is discussed by Brandle,[15] who states that post-traumatic atrophy appears during the second to fourth week in 85% of the cases. Fifty-seven patients were reported. Wolter and Liss [16] describe histopathologic changes in the optic nerve produced by indirect compression, reporting two cases. The pressure resulted in astrocytic hypertrophy and proliferation and finally degeneration with connective tissue replacement.

In an article discussing preretinal and optic nerve sheath hemorrhage in the presence of subarachnoid bleeding, Smith, Kearns, and Sayre [17] confirm the present opinion that intraocular and optic nerve sheath hemorrhages do not arise from nerve sheath extension from concurrent subarachnoid hemorrhage but occur as separate and independent hemorrhages, probably as the result of increased venous pressure resulting from sudden increased intracranial pressure.

Blood Supply to the Visual System

The blood supply to the visual system is receiving further study. François, Neetens, and Colette [18] continue to provide us with the products of their painstaking work in their fourth report, the vascularization of the optic pathway, the optic tract, and the lateral geniculate body. They found from injected specimens that the chiasm is supplied chiefly by the anterior carotids, anterior cerebrals, and anterior communicating arteries. Francois * describes an anterior chiasmal artery, found in about one-third of the material examined, arising from the anterior communicating artery passing to the optic chiasm. Brodie Hughes * calls attention to lateral chiasmal arteries, first described by Dawson, arising from the internal carotids and passing to the optic chiasm. François continues the study with the report that the optic tract receives its supply from both the anterior choroidal and posterior communicating arteries. The external geniculate body is supplied chiefly by the posterior cerebral and less by the anterior choroidal arteries.

Steele and Blunt [19] provide an elaborate demonstration of the vascular anatomy and the blood supply to the optic nerve and chiasm in man. Shea [20] describes the anastomoses between the external and internal carotid systems. Remky [21] reports his experimental work on the adjustment of the cerebral circulation to normal exertion as seen through observation in changes in the retinal circulation, with the use of the Bailliart ophthalmodynamometer.

Rezanov [22] describes the role of the central nervous system through observance of

* Personal communication to the author.

the permeability of the vessels of the eye. He noted that depressants and stimulants of the nervous system affected permeability of the ocular vessels, possibly through trigeminal or neurohumoral mechanism.

Alexander [23] makes an important contribution regarding the association of the visual functions and the aphasias in vascular lesions affecting the visual pathways. He found homonymous hemianopsia associated with other functional changes, either stimulative or destructive, which, considered together, localize the lesion. Affections of the temporal isthmus and temporal lobes are discussed in detail. The study of vascular lesions, their diagnosis, and their localization has been greatly aided by angiography. Erausquin, Oribe, and Zimman,[24] emphasizing the diagnostic importance of cerebral angiography in ophthalmological syndromes, review the literature and describe the anatomy and technique.

With improved technique, and better understanding of the vascular anatomy and circulation, reports of serious consequences of angiography are rarely found. Fink [25] describes a patient who developed sudden transient hemiplegia and blindness with confabulation and disorientation. These symptoms, comprising Anton's syndrome, are found in patients with cortical degeneration, the so-called cerebral blindness usually produced by various sclerosing processes.

Aneurysms

From an intensive study of 119 cases of intracranial arterial aneurysms, with special reference to the ocular findings, Henderson [26] has assembled statistics. The age group lies between 31 and 50; the sexes are equal; caudal aneurysms are five times as frequent as rostral; most cases showed evidence of subarachnoid hemorrhage. Arteriography established the diagnosis in 94.5% of the cases. Retinal and subhyaloid hemorrhages were found with subarachnoid hemorrhages, frequently with papilledema. Oculomotor paralysis was another rather constant symptom.

Minton [27] discusses intracranial aneurysms of the internal carotid and cerebral arteries and presents a detailed report of five patients. Gallagher, Dorsey, Stefanini, and Looney [28] present a case report, a rare occurrence of a large intracranial aneurysm producing hypopituitarism and the frontal lobe syndrome. The second, third, fourth, and sixth nerves were involved. The authors state that this is the first case reported in which the symptoms of hypopituitarism, hypogonadism, and hypothyroidism were found.

Manghi and Saginario,[29] in a study of 11 cases of intracranial aneurysm, found an isolated third-nerve paralysis in about one-third of the cases. Reporting on 75 patients with aneurysm arising at the internal carotid-posterior communicating artery junction, Harris and Udvarhelyi [30] found 25 with oculomotor paralysis. Their angiographic studies are described together with the symptoms and treatment.

Lincoff and Cogan [31] write of unilateral headache and oculomotor paralysis not caused by aneurysm. Rand [32] studied retinal arterial pressure in the presence of cervical carotid artery occlusion in the treatment of cerebral aneurysms. From his studies he concludes that a decrease in retinal arterial pressure is a direct indicator of reduced carotid circulation. He believes that if retinal arterial pressure drops 50% or less the prognosis is grave.

Erdbrink [33] studied a case of subclinoid aneurysm of the internal carotid artery with the diagnostic aid of angiography. The lesion was located in the posterior portion of the cavernous sinus, involving the sixth nerve. Bitemporal field loss was found, and there was contralateral numbness in the upper extremity.

The syndrome of so-called pseudoglaucoma in a patient with intracranial arterial aneurysm is described by Quintieri.[34] This patient had normal intraocular pressure with cupped and pale papilla, bilateral nasal field loss, and central scotoma. An angiogram

revealed bilateral aneurysmal dilation of the carotid arteries.

The anatomy of the middle fossa in relation to the cavernous sinus and chiasmal cistern is discussed by Taptas,[35] who presents his views of pathology in that area. Walker and Allegre[36] review the history and symptomatology of carotid-cavernous fistulae and report 24 cases treated surgically. The syndrome of pulsating exophthalmos, bruit audible to both patient and examiner, and, less frequently, ocular pareses produced by trauma, ruptured aneurysm, and congenital anomaly is discussed. Serfling and Parnitzke[37] describe the anatomy, etiology, symptomatology, diagnosis, and treatment of arteriovenous fistulae. They found a very few cases resulting from arteriosclerosis and syphilis.

Vascular Occlusion

One must consider the possibility of thrombosis of the internal carotid artery, as stated by Nielsen,[38] in all cases of transient aphasia or hemoplegia, in all cases of intermittent amaurosis with findings of ophthalmic artery occlusion, in all cases of neck trauma, and in arteriosclerosis of various types. Korbin[39] cites two cases of thrombosis of the internal carotid artery in the neck confirmed by angiograms, with homonymous hemianopsia and bouts of numbness.

In addition to angiography, determination of retinal arterial pressure is being more frequently reported as aid in the diagnosis of carotid artery occlusion. This is discussed by Heyman, Karp, and Bloor.[40] Retinal dynamometry and provoked obstruction in a case of carotid thrombosis with delayed symptomatology is described in a patient by Bronner and Heinrich.[41]

Cranial bruit associated with occlusion of the internal carotid artery best heard by listening over the contralateral eyeball is a very useful diagnostic sign according to the study of Fisher,[42] who attributes this to increased circulation in the remaining patent artery.

The anatomical structure of the cavernous sinus is described in detail by Taptas.[35] Orbital decompression for aseptic cavernous sinus thrombosis to prevent optic atrophy, proptosis, and ophthalmoplegia due to venous obstruction and orbital pressure is discussed by Kaiser.[43]

Diagnosis, treatment, and complications of cavernous sinus thrombophlebitis are discussed by Taylor.[44] The causative agent in two cases reported was Micrococus pyogenes var. aureus (Staphylococcus aureus). The recommended treatment is penicillin and anticoagulants.

Homonymous hemianopsia following division of the parieto-occipital vein is described in three cases by Welch.[45] He states that the recovery of the lost field is expected through collateral circulation, which occurred in the two patients who survived.

The syndrome of vertebral artery compression or occlusion consisting of pain in back of the neck or occipital region, vertigo, and nystagmus is discussed by Tatlow and Bammer.[46]

Cortical Lesions

Ettlinger[47] discusses sensory deficits in visual agnosia, reporting 30 cases. The results do not support the view that agnostic conditions are secondary to defective visual sensory discrimination. Nielsen and Carnes[48] report a patient with visual agnosia for inanimate objects produced by a left-sided vascular lesion. There was also finger agnosia and disturbance of body scheme. A lower right quadrantanopsia was present. The presence of agraphia and astereognosis indicated a parietal lobe lesion. Drew[49] gives a neurologic appraisal of familial congenital word-blindness and concludes that a defect in recognition may be due to delayed development of the parietal lobe. The subject is thoroughly reviewed.

The parietal lobe syndrome is described by Selby,[50] in which the adjacent occipital and temporal lobes are also involved with production of visual hallucinations, homon-

ymous field loss, and visual psychic disturbances.

Benton [51] states that early symptoms of the Gerstmann syndrome (parieto-occipital syndrome) produce visual disorientation from involvement of the higher visual centers of the posterior parietal and bordering occipital lobe. The symptoms are finger agnosia, spacial disorientation, dysgraphia, dyscalcula, dyspraxia, color agnosia, and visual agnosia.

The psychologic significance of visual auras is described in a study of three cases of brain damage with seizures by Beck and Guthrie.[52] They state that visual aura, in a sense, is analogous to dream content and is not a manifestation of occipital or frontal lobe lesions.

A differential diagnosis between hysteria and malingering is described by Lincoff and Ennis [53] in a psychiatric study. Bellavia [54] presents a patient with ocular hysteria with absolute mydriasis, absence of pupil reflexes, and loss of accommodation.

Visual Fields

Harrington [55] has produced an excellent book on visual fields, well presented and beautifully illustrated, a valuable study and reference. An editorial of interest on the evolution of clinical perimetry is written by Lebensohn.[56] Fields and functional disease are discussed by Linhart,[57] who presents well-documented cases of neuroses and hysteria and their relation to mental stress in mental cases with ocular symptoms.

Diez and Androgrie [58] discuss altitudinal (horizontal) hemianopia and enumerate the causes and location of the lesions from a study of 24 cases.

Eleven patients were examined and visual fields were reported by Glees and Zielinski,[59] who found scotomata in optochiasmatic arachnoiditis, adenoma of the pituitary, parasellar meningioma, and epidermoid of the third ventricle.

Ocular Muscles

Cogan's [60] second edition of "Neurology of the Ocular Muscles" is an excellent amplification of his first valuable edition, with added chapters on myopathies and discussion of new investigations.

In an article on the physiological basis of sensory fusion Rønne [61] states that integration of visual images takes place in the occipital cortex. Stereopsis, integration of disparate impulses, and retinal rivalry are products of this area.

Keiner,[62] in a paper on physiology and pathology of the optomotor reflexes, discusses their development and disturbances affecting them and describes various types of strabismus, disorders of conjugate reflexes, and types of nystagmus. It is worth while reading Adler's discussion of this presentation, which appears at the end of the article.

Disturbance of ocular motility in relation to supranuclear lesions is discussed by Tour,[63] who describes version and disjunctive action and the effect of lesions producing various symptoms and syndromes.

From his intensive study, Warwick [64] describes the organization of the oculomotor, trochlear, and abducens nerves regarding their muscular innervations. He finds a difference from the usually accepted opinion in the innervation of the third nerve. He further states that Perlia's nucleus is not a convergence center. He finds the parasympathetic pathway to be the same as described by other investigators.

Rucker, Dyer, Smith, and Taub [65] discuss ocular muscle paralysis from a large source of material, consisting of 653 cases. The series is large enough to provide statistical data. From a statistical review and analysis of 604 cases, Sanna [66] discusses the etiology and frequency of external ocular paralysis, finding congenital causes and infection more frequently in childhood; trauma, in middle life, and tumors and vascular affections, in the aged.

McAuley [67] finds progressive external ophthalmolplegia, apparently with hereditary tendency, to be a part of generalized progressive muscular dystrophy. He reports four cases.

Disturbance of eye movements as a neurologic problem is discussed by List,[68] who describes infranuclear, internuclear, and supranuclear oculogyric function and dysfunction of version, vergence, and duction.

In an article on vascular phenomena involving brain stem structures, Fang and Palmer[69] describe conjugate gaze palsies and visual impairment in occlusion of the basilar artery. Four cases of unilateral internuclear ophthalmoplegia of vascular origin are described by Fine and MacGlashan,[70] who agree with the predominating opinion of anterior and posterior types. Hedges and Adler[71] present three cases of brain stem lesions with oculomotor manifestation produced by internuclear ophthalmoplegia.

Continuing the contribution to their study of eye movement responses, Westheimer and Mitchell,[72] having formerly discussed conjugate movements, present their studies of disjunctive eye movements (vergence) with photographic recording. Alpern and Wolter[73] discuss the relation of horizontal saccadic and vergence movements and present the concept that the final common pathway for vergence movements courses along thin autonomic nerve fibers and that for saccadic (jerk) movements, along thick somatic nerve fibers.

A discussion of congenital ocular motor apraxia is presented by Reed and Israels.[74] The condition consists of normal vertical conjugate eye movements with impaired lateral movements, with head jerking in the direction of the intended object of gaze, the eyes rotating to the opposite side. With a report of three cases, Lewis[75] describes the syndrome of hereditary congenital ophthalmoplegia consisting of bilateral ptosis, absence of vertical eye movements, and marked reduction or absence of horizontal movements.

Volk and Bruell[76] describe eye movements in a patient with cerebral hemispherectomy. They conclude that there is definite evidence that voluntary (and reflex) eye movements in all directions, as well as convergence, are possible with only one functioning cerebral hemisphere.

A clinical contribution to the study of recurrent and alternating external ophthalmoplegia is provided by Mannironi and Toselli.[77] Their studies with EEG show rapid rhythms which characterize tumors of the lower brain stem through activated oculogyric nuclei or tracts.

The effect of alcohol on the motor fusion reserves and stereopsis as well as on the tendency to produce nystagmus is discussed by Seedorff.[78] There is a marked difference of tolerance, but all subjects showed deterioration of motor and sensory function.

McCarthy[79] describes ocular and palatal myoclonus and presents a case. He states that the myoclonic triangle includes the inferior olive nuclei, dentate nuclei, central trigeminal tracts, and cerebellar peduncles. Stimulation of this area produces myclonic movements in which ocular movements participate.

Ocular nerve paralysis with headache is described by Jackson,[80] with a report of four cases, and by Harris-Jones,[81] who reports three cases. In a discussion of unilateral headache and oculomotor paralysis Lincoff and Cogan[82] enumerate and describe various causes, which include diabetes, paraclinoid tumors, leukemia, and ophthalmoplegic migraine. Dreyfus, Hakim, and Adams[83] suggest that the cause of diabetic ophthalmoplegia may be the occlusion of the nutrient blood supply to the nerve.

The genesis of pathological associated movements after paralysis of the facial and oculomotor nerve is discussed by Leonhard.[84] He rejects the theory of misdirected fibers. Jain[85] writes on abnormal lid retraction, citing nine cases, most frequently of congenital origin. A book by a number of contributors on regeneration of the central nervous system has been edited by Windle.[86] In their investigation it was found that in both animals and man regeneration can definitely occur, and this statement is supported by an excellent presentation.

Rowland and Eskenazi [87] review 39 fatal cases of myasthenia gravis, including a case of almost complete ophthalmoplegia. These patients responded to edrophonium (Tensilon) and neostigmine and showed marked sensitivity to curare. The rare condition of congenital myasthenia gravis with ophthelmoplegia is presented by Heinzen and Baasche.[88] The authors recommend neostigmine (Prostigmin) tests for all cases of congenital ptosis and external ophthalmoplegia.

Inquires into the physiology of optokinetic nystagmus are the subject of an article by Mackensen.[89] He states that changes in the form of the oscillation are dependent on the velocity of the stimulus. Tests were made at various speeds. Enoksson [90] discusses optokinetic nystagmus in brain lesions. He finds normal reaction in lesions of the optic nerve and chiasm. Lesions of the cerebral hemisphere frequently produce decrease of nystagmus, or perhaps irregular nystagmus, on rotation toward the side of the lesion. In lesions of the posterior cranial fossa nystagmus is reduced, with the rotation away from the side of the lesion. Optokinetic nystagmus may be of value in locating the laterality of the lesion. Unger [91] discusses behavior of optokinetic nystagmus in psychogenic visual disturbances. He supports Bing's view that hysterical reactions at organically or functionally grounded pathways may interfere with the production of optokinetic nystagmus. This may serve as a test to differentiate between hysteria and malingering.

Aschan, Bergstedt, Goldberg, and Laurell [92] suggest vestibular origin for alcoholic positional nystagmus.

The Pupils

The Argyll Robertson pupillary syndrome is described by Lowenstein,[93] who enumerates the various sites which have been suggested for the location of the lesion. He suggests that the lesion is in the prenuclear afferent pupil arc in the vicinity of the oculomotor nucleus. Lowenstein [94] also, in another article, details his pupillographic studies of dark-adapted patients with Argyll Robertson syndrome and related pupillary disorders. These conditions are characterized by miosis from damage to the sympathetic pupillary fibers and supranuclear pathways ending in Edinger Westphal's nucleus and from parasympathetic spasm.

Pupillary changes in the Holmes-Adie syndrome is described by Russell,[95] who presents four cases. He believes that the main defect is due to parasympathetic denervation, the sympathetic remaining intact, and locates the lesion in the efferent parasympathetic pathway, probably postganglionic. He suggests two types, parasympathetic and tonic. Cristini [96] believes that the lesion of Adie's syndrome is ciliary ganglionitis. He describes cases to support his view.

Following a phrenic crush with damage to the sympathetic nervous system Horner's syndrome was produced. This case is described by Chatterjee.[97] Eurico Ferreira and Alves Sampaio [98] review the history of Horner's syndrome and present cases.

Autonomic Nervous System

Frey [99] furnishes us with new anatomical data on the phylogenetic aspects of visual function with the report of his study of the association of the hypothalmus and visual system in animals and humans. He describes nuclear vegetative centers and nerve fiber paths coursing in the optic nerves, chiasm, and tracts. The degenerative changes resulting from enucleation are described. Experimental aspects of nervous control of the ocular circulation and intraocular pressure are presented by Perkins.[100] The investigation suggests definite sympathetic (diencephalic) control of ocular circulation, which influences aqueous formation. Sensory (fifth nerve) stimulation also seemed to have some similar influence. Third and seventh nerve stimulation did not result in altered intraocular tension or vascular changes in the eye.

Further studies associating diencephalic function and lesions with intraocular tension and glaucoma are reported. Thalamocortical pathogenesis of glaucoma is discussed by Radovici,[101] who supports Magitot's conception. He enumerates the mechanical, vascular, and neurohumeral theories. Marty [102] describes the relation between glaucoma and hypophyseal adenomata. There was mention of pseudoglaucoma or low-tension glaucoma, the ophthalmoscopic appearance of the papilla showing pallor and cupping. Visual fields and x-rays should be of aid in establishing the proper diagnosis but are not always. Lowenstein [103] speaks of the diencephalon and primary glaucoma, in which he believes there is a characteristic pupillary syndrome. Cavka [104] reviews the literature and discusses the frontal and diencephalic regulating center in glaucoma. Encephalographic and ventriculographic studies showed atrophy of cerebral structures. The author suggests inflammation or intoxication leading to atrophy in the frontal diencephalic structures, which affects the neurovegative system, with the production of glaucoma.

Autonomic dysfunction producing ocular manifestations of the Riley-Day syndrome includes corneal involvement of varying severity with absence of psychic tearing. This affection was discussed by Liebman.[105] It appears to me that the so-called trophic innervation of the cornea is disturbed together with autonomic influence of lacrimation.

Facial Nerve

Discussing ocular considerations in facial paralysis, Cowan [106] reviews the anatomy and classification of types of involvement, with suggested treatment. Sprofkin and Hillman [107] present two patients with Moebius' syndrome (congenital oculofacial paralysis). They concur in the prevailing belief that nuclear hypoplasia, as the causative factor, is most plausible.

Electrophysiologic and clinical observations in hemifacial spasm are presented by Weil and Nosik,[108] who report eight cases. They state hemifacial spasm resulting from cortical irritation is uncommon. It is more frequently found with lesions of the facial nucleus or its branches, showing a characteristic electromyographic pattern. However, the site of greatest clinical disturbance does not always correspond with that of the electromyographic disturbance. Hemifacial spasm of psychogenic nature (habit spasm) is the most frequent type. It may be unilateral or bilateral and can be abolished by intravenous sodium Amytal. In this type the electromyographic charts are identical with those found with normal voluntary movements.

Electromyography is a tool, according to Breinin,[109] in ocular and neurologic diagnosis. It may aid in differentiating between myasthenia gravis, extraocular muscle paralysis, nuclear ophthalmoplegia, and nystagmus.

Trigeminal Nerve

Raeder's paratrigeminal syndrome, according to the original description, consists of a lesion in a circumscribed area containing the sympathetic nerve to the ocular structures, the damage to which produces Horner's syndrome. In addition, the cranial nerves to the eye and orbit and the trigeminal nerve are involved, with damage to the latter, producing sensory disturbances. Klingon [110] questions the use of the term paratrigeminal, especially its localization in a relatively small area. He presents a case and reviews the literature.

Bonnet [111] speaks of the trigeminal sympathetic syndrome, trigeminal sympathetic neuralgia, and the cavernous syndrome.

Observations on the pain and trigger mechanism in trigeminal neuralgia are made by Crue, Shelden, Pudenz, and Freshwater.[112] This article on tic douloureux describes posterior root compression treatment as well as decompression and reports eight cases operated upon with relief and with no recurrence or complications. Taarnhøj [113] speaks of trigeminal neuralgia and decompression of the trigeminal root

for its relief. Decompression and compression operations for trigeminal neuralgia are discussed by Behrman and Knight.[114] They observed that postoperative herpes was not noted in the ophthalmic division and, while recurrent herpes simplex on rare occasions involved all three divisions of the trigeminus, the two lower divisions were affected much more frequently than the ophthamic. If the ophthalmic division was involved, the cornea was usually affected.

In my experience, the cornea is always affected immediately following trigeminal surgery of any type when the ophthalmic or maxillary divisions are implicated. This is evidenced by the hazy corneal epithelium seen with the biomicroscope and the staining throughout with fluorescein. The condition gradually disappears, usually in the course of hours or days, excepting on rare occasions when so-called trophic disturbances continue.

Gamazo-Ferdinandez and Ignacio-Valentin[115] review the literature of ophthalmic migraine and describe the etiology, symptoms, diagnosis, and treatment. Roentgenographic findings in trigeminal neuralgia are described by Gardner and Todd.[116]

Perkins,[117] stimulating the trigeminal nerve in rabbits, found that the pupil contracts, there is a rise in temperature of the ciliary region, and there is a rise in intraocular pressure, with increase of aqueous protein. Sectioning gives the same immediate effects.

Demyelinating Diseases

A survey of Devic's disease is made by Wagner.[118] He describes the symptoms of pain behind the eye; rapid loss of vision; dilated, frequently fixed, pupils, and slight papilledema. Two cases are reported. Keefe and Trowbridge[119] discuss neuromyelitis optica with increased intracranial pressure, which is rarely found.

Orban[120] presents data concerning opthalmoscopic changes and other symptoms of multiple sclerosis. He found sheathing of the retinal veins in 40% of the cases and believes that this condition is analogous to sheathing of cerebral vessels. Low and Carter[121] write of multiple sclerosis in children, describing typical cases confirmed at necropsy. Seven cases were reported. The predominating symptoms were third nerve paralysis, retrobulbar neuritis with diplopia, and reduction or loss of vision.

Infections

A review of optochiasmatic arachnoiditis is presented by Sonntag,[122] who discusses symptoms, prognosis, and treatment. Prompt surgical intervention is urged. The ophthalmologic findings are discussed by Niebeling,[123] with the report of 16 cases surgically verified. Perez-Llorca and Lopez-Porrua[124] review the subject of optochiasmatic arachnoiditis and present a case with binasal hemianopia relieved by surgery. A differentiation between optochiasmatic arachnoiditis and Leber's disease with a report of four cases and review of the literature is presented by Scassellati Sforzolini.[125]

Marin Amat[126] discusses the ocular manifestations in 100 cases of tuberculous meningitis, with a classification of symptoms. Fundus changes were seen in all. Pupil action and extraocular motility are discussed. Alajmo[127] believes that changes in the papilla as mainfested by edema, congestion, and atrophy in the presence of miliary choroidal tubercles may be due either to direct involvement of the optic nerve or, indirectly, to optochiasmatic arachnoiditis. Diagnosis and treatment are discussed.

Transient glaucoma in viral encephalitis with diencephalic lesions is reported by Krieger and Feigen,[128] citing a patient who developed acute intraocular hypertension with encephalitis. They suggest that this may point to the diencephalon as a control area for intraocular tension.

Stephens and Welch[129] describe a patient with retinal vascular thrombosis in the presence of subdural abscess. This is in line with previously described cortical vascular thromboses produced by subdural abscess.

Homonymous hemianopsia after carbon monoxide intoxication is described by Danis and Toussaint.[130]

Potts[131] talks of the toxic amblyopias and believes, in view of recent investigation, that the term is not correct and should not be used. He believes that most toxic conditions are due to acidosis, anorexia, and other metabolic and nutritional disorders.

Tumors

Tumors of the optic papillae are discussed and classified by Wagener.[132] Although it bears only occasionally on intracranial associations, this excellent review should not be overlooked. Gramberg-Danielsen[133] attempts to classify the morbid anatomy of primary tumors of the optic nerve in a similar manner to that of brain tumors.

A review of gliomas of the optic nerve is presented by Hanbery,[134] who states that 90% of the cases occur before the age of 20. The prognosis is good if there is no intracranial extension. One must consider the association of neurofibroma and aplasia of the orbital bone as possibly accompanying conditions. Slade and Weekley[135] describe glioma of the optic tract, which is rarely reported.

The value of radiation therapy in the management of glioma of the optic nerves and chiasm is discussed by Taveras, Mount, and Wood.[136] They state that the results are good, with possibility of retention and even improvement of vision. They suggest surgery for diagnosis and relief of cerebrospinal fluid obstruction.

Meningioma (dural endothelioma) of the optic tract is discussed by Dunn and Walsh,[137] who comment upon its slow growth, absence of interference with orbital movement, and enlargement of the optic foramen, which is not necessarily present. Razumikhina[138] presents a patient with meningioma of the optic nerve with rare extension into the disc. An unusual cause of visual loss produced by meningioma in both optic foramina is discussed by Petr and Sercl.[139] A child aged 3 years having a primary meningioma in the orbit with invasion of the optic nerve is reported by Martin and Schofield.[140]

Grant and Heges[141] describe ocular findings in meningiomas of the tuberculum sellae. They review the literature and the study of 30 cases in which visual symptoms were the initial and most important observations. Slow progressive loss of vision with optic atrophy is characteristic. Papilledema is not present. X-rays may be negative. Arteriography may be of aid.

A book by Huber[142] on ocular symptoms in cerebral tumors is well worth reading. It is replete with interesting clinical cases. Bonnet[143] writes on ophthalmological signs of cerebral tumors and emphasizes the necessity of visual field study. He discusses lesions of the optic pathways and types of ocular palsies. Kroll[144] stresses the importance of ocular signs in the diagnosis of brain tumors and discusses 125 cases.

The ocular signs of tumors involving the anterior visual pathways were enumerated by Walsh.[145] He describes intrinsic and extrinsic tumors of the optic nerve and chiasm according to type, with case reports of clinical examination and laboratory findings. Grövall and Silver[146] report on a series of 167 cases of intracranial tumors and describe their symptoms and classification.

Kizelman[147] finds that there is a change of caliber of the retinal vessels in brain tumors. He finds in 75% of the cases narrowing of the arteries and dilating of the veins to the extent of 25μ. He states that they return to normal caliber after removal of the tumor.

Pressure on the visual pathway producing field changes from various tumors such as meningioma, craniopharyngioma, and chromophobe pituitary adenoma is discussed by Dolenek, Mikula, Klaus, and Zapletal,[148] who enumerate aids to early diagnosis of intracranial tumors causing primary optic atrophy.

Pituitary adenoma, carcinoma, and craniopharyngioma are discussed by Wise, Brown, Naffziger, and Boldrey,[149] who describe the symptoms and classification of 172 cases, with diagnosis and treatment.

Sudden loss of vision from hemorrhage into pituitary adenomata is described by Uehlein, Balfour, and Donovan.[150]

Syphilitic gumma of the hypophysis is described by François and Verriest.[151] The symptoms were bitemporal hemianopsia and signs of pituitary dysfunction. The visual loss improved with treatment. A patient with chordoma of ophthalmologic interest is presented by Dyson.[152] History and description of this rare tumor is given, with clinical findings. The tumor arose within the dorsum sellae.

Ophthalmological aspect of tumors of the temporal lobe is discussed by Schweitzer,[153] with description of the pathognomonic symptoms. The author feels that no satisfactory explanation exists for the presence of upper quadrantanopia.

Cutler [154] presents two cases and describes the ocular manifestations of lethal midline granulomata with involvement of orbital structures.

Rintelen [155] describes the ophthalmologic symptoms and syndromes in cases of infratentorial cerebral tumors, with a discussion of the function and dysfunction of the brain stem and cerebellum.

Pseudotumor cerebri is described by Davidoff [156] as a syndrome of increased intracranial pressure producing headache and papilledema, usually without other neurologic manifestations. He states that the etiology is unknown and probably variable. The discussion is based on his experience with 61 cases.

Spontaneous hematoma of the cerebellum and hematoma of the fourth ventricle with eye symptoms are presented by Outes and Martino.[157] The study of symptoms resulting from cerebellar hemorrhage and the establishment of a syndrome which can be recognized early, according to the authors, will prevent loss of life by timely operative intervention.

Riggs and Yaskin [158] describe a cranial nerve syndrome associated with nasopharyngeal malignancy. In a series of 11 cases extraocular paralysis was found in all but 1.

McBride and Elsey [159] discuss the value of the midline planigram for diagnosis of midline tumors, reporting a case of adenocarcinoma of the optic chiasm.

Injuries

Benda and Hoessly [160] describe birth injuries and cerebral trauma in early childhood which produce damage to the visual system. Results of early surgical intervention in amaurosis secondary to cranial trauma are discussed by Martelli and Strazzi,[161] who advocate prompt relief of pressure on the optic nerve by unroofing the canal. I have, in my experience, never seen benefit from this operation insofar as vision is concerned, but perhaps surgery was delayed too long. The question of traumatic lesions of the chiasm is discussed by Zintz.[162] There are usually sagittal tears from blows on the skull, resulting in bitemporal hemianopsia and neighborhood pituitary and hypothalamic symptoms.

Rosenberg [163] describes post-traumatic cortical blindness, the so-called cerebral blindness, with active pupils and negative ophthalmoscopic examination. The oculogyric system is usually spared. Areas 17, 18, and 19 of Broadmann may be affected so that visual fields may be involved and recognition and perception of objects may be faulty. The patient with cortical degeneration may deny total blindness. This is Anton's syndrome.

Miscellaneous

A discussion of the association of the eye with the brain is presented by Kearns,[164] who describes the effect of tumors, cardiovascular disease, and multiple sclerosis upon ophthalmologic structures.

Jaeger [165] discusses eye disorders associated with surgical problems of the nervous system in an excellent presentation.

Neuro-ophthalmological examination in children is discussed by Hollenhorst.[166] Methods of visual and oculogyric examination are described in detail. Ophthalmological observations in craniosynostosis are made by Laitinen, Miettinen, and Sulamaa,[167] with a review of the literature and description of the conditions. They conclude that operation has a beneficial effect. Gross [168] gives data concerning atrophy of the optic nerve in turrecephaly, the result of inhibition of longitudinal growth of the brain due to defects in skull development.

A pathologic study of a patient with amaurotic family idiocy is made by Shapira and Leight,[169] in which they found lipid degeneration of the ganglion cells of the retina and central nervous system. Hanhart [170] presents 27 pedigrees of infantile amaurotic idiocy. He concludes that Jews are not the only ones affected and that there is an autosomal recessive inheritance. Other types of lipoidosis were not seen in these patients or other members of the family.

Two patients, female siblings, are presented with pigmentary retinal lipid neuronal heredodegeneration (Spilmeyer-Vogt disease) by Hoffman.[171] The symptoms, he states, begin at about the age of 6 years. The author believes that the disease is a separate entity and hereditary process of the nervous system. Progressive retinal degeneration and ataxia is described by Björk, Lindblom, and Wadensten.[172] The Kayser-Fleischer rings found in two patients with hepatolenticular degeneration were examined and observations were made in relation to the pathogenesis and clinical appearance by Uzman and Jakus.[173]

Hypophysectomy is being performed in two conditions affecting the eyes. It has been done for the treatment of malignant edematous exophthalmos as described by Voisin, Albeaux-Fernet, Guiot, and Haye.[174] Hypophysectomy has been done with the hope of restoring vision in severe diabetic retinopathy with retinal and vitreous hemorrhages as described by Schimek,[175] who reports five cases treated, with cessation of visual loss from ocular hemorrhage.

Lossius [176] tells of transitory visual disturbances after ventriculography in three patients who experienced dimness of vision and left inferior homonymous quadrantanopia. He believes this to be caused by vasomotor action on cerebral vessels.

As this manuscript was being completed, the second edition of Walsh's [177] "Clinical Neuro-Ophthalmology" was laid on my desk and as I turned the pages of this monumental work in anticipation of the great benefit I would derive from its contents I was once again overwhelmed by the extent of this tremendously valuable contribution.

411 Oak St. (19).

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News and Comment

GENERAL NEWS

New York Society for Clinical Ophthalmology.—The officers of the New York Society for Clinical Ophthalmology for the coming 1957-1958 season are the following: President, Harvey E. Thorpe; Vice-President, Arthur Linkz; Recording Secretary, Jesse M. Levitt; Corresponding Secretary, Leon H. Ehrlich; Treasurer, Henry M. Kera.

Committee chairmen are the following: Program, Abraham Schlossman; Instructive Session, Alfred Kestenbaum; Legislative, Benjamin C. Rosenthal; Membership, Howard Agatston; Industrial, Edward M. Douglas.

Dr. Max Chamlin, the retiring president, was elected to the Advisory Council.

American Ophthalmological Society Officers.—At its recent meeting the American Ophthalmological Society elected the following officers for the coming year. President, Dr. Walter S. Atkinson, Watertown, N. Y.; Vice-President, Dr. Derrick Vail, Chicago; Secretary-Treasurer, Dr. Maynard C. Wheeler, New York; Editor of the Transactions, Dr. Gordon M. Bruce, New York.

Eye Section, New Jersey Academy of Ophthalmology and Otolaryngology. The following are the officers and directors of the Eye Section, New Jersey Academy of Ophthalmology and Otolaryngology, 1957-1958.

Officers: President, Dr. Irvin Levy, Trenton, N. J.; President-Elect, Dr. Edward A. Atwood, Paterson, N. J.; Vice-President, Dr. Louis A. Amdur, Jersey City, N. J.; Secretary, Dr. Alfonse A. Cinotti, Jersey City, N. J.; Treasurer, Dr. Oram R. Kline Jr., Camden, N. J.

Directors: Dr. Ralph E. Siegel, Perth Amboy, N. J., 1958; Dr. Laurence C. Griesemer, Elizabeth, N. J., 1958; Dr. Raymond C. Collins, East Orange, N. J., 1959; Dr. Samuel Diskan, Atlantic City, N. J., 1959; Dr. Henry Abrams, Princeton, N. J., 1960; Dr. Vincent A. Burell, Phillipsburg, N. J., 1960.

Past President: Dr. Charles E. Jaeckle, East Orange, N. J.

The above officers constitute the Council of the New Jersey Ophthalmological Society.

ANNOUNCEMENTS

Ohio State Postgraduate Course in Ophthalmology.—A postgraduate course in ophthalmology is being offered at The Ohio State University, Ohio State Union Building, March 3 and 4, 1958. Registration is at 8 a. m. Monday, March 3, 1958, at Ohio Union Building, Conference Theater. The registration fee is $20.00. Registration by mail is desirable. Address all inquiries to William H. Havener, M.D., Department of Ophthalmology, University Hospital, Columbus 10, Ohio.

The program of the course is as follows.

Monday, March 3: Registration; Intraocular Malignant Melanoma, Dr. William H. Havener, Ohio State University; Intraocular Diseases Simulating Melanoma, Dr. Algernon B. Reese, New York; Enucleation, Evisceration, Exenteration, Dr. F. Bruce Fralick, University of Michigan; Incidence of Unsuspected Melanoma, Dr. Torrence A. Makley, Ohio State University; Stereoscopic Indirect Ophthalmoscopy for the Diagnosis of Intraocular Tumors, Dr. Charles L. Schepens, Boston; Surgical Errors in the Management of Tumors, Dr. Fralick; dinner meeting with Columbus Academy of Eye, Ear, Nose, and Throat; Orbital Tumors, Dr. Reese.

Tuesday, March 4: Movie, Embryology of the Eye; Principles of Lid Surgery, Dr. Fralick; Radiotherapy of Eye Lesions, Dr. Reese; Retinal Detachment, Dr. Schepens; Retinoblastoma Inheritance, Dr. Madge T. Macklin, Ohio State University; Retinal Detachment, Dr. Schepens; Sinus Neoplasms, Dr. William H. Saunders, Ohio State University. A program has been planned for wives.

Association for Research in Ophthalmology: Call for Papers.—The next meeting of the Eastern Section of the Association for Research in Ophthalmology will be held in Wilson Hall of the Administration Building, at the National Institutes of Health, Bethesda 14, Md., on Jan. 16, 17, and 18, 1958.

The first part of the meeting will consist of a symposium on electrophysiology of the visual system, which is planned to present a cross section of work in this general area. This symposium is sponsored by the National Institute of Neurological Diseases and Blindness and will be followed by presentation of free papers by nonmembers as well as members of the Society.

Titles and abstracts of papers to be presented at this meeting should be based on research and not be of a clinical nature in the usual sense. Most likely, 15 minutes will be allowed for each paper. Abstracts should be in a form suitable for printing in an ophthalmology journal without further editing. Forms will be sent on request. Publication of the papers is not required, however. Write to Ludwig von Sallmann, M.D., Local Chairman, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Md.

Postgraduate Training in India.—Sitapur Eye Hospital, India, offers facilities for postgraduate training in ophthalmology, particularly in operative surgery, for two months at a nominal fee of $1000, which includes board and lodging. The course begins on Jan. 1, 1958. Apply to the Chief Surgeon, Eye Hospital, Sitapur, U. P., India, at an early date.

Association for Research in Ophthalmology: Future Meetings.—The Association for Research in Ophthalmology announces the following future meetings. Letters of intention to present papers may be immediately sent to the chairman of each meeting.

Western Section: San Francisco; Nov., 1957; Levon Garron, M.D., Chairman, 426 17th St., Oakland 12, Calif.

Southern Section: Miami Beach, Fla.; Nov. 12, 1957; Sherman B. Forbes, M.D., Chairman, 706 Franklin St., Tampa 2, Fla.

East Central Section: Cleveland; Jan. 7, 1958; Albert M. Potts, M.D., Chairman, University Hospitals, 2065 Adelbert Rd., Cleveland 6.

Eastern Section: Bethesda, Md.; Jan. 16, 17, 18, 1958; Ludwig von Sallmann, M.D., Chairman, National Institutes of Neurological Diseases and Blindness, Bethesda 14.

Midwestern Section: St. Louis; April 21, 1958; Bernard Becker, M.D., Chairman, 640 S. Kingshighway Blvd., St. Louis.

National Meeting: San Francisco; June, 1958; Lorand V. Johnson, M.D., Secretary, 10515 Carnegie Ave., Cleveland 6.

With the object of reducing the number of sessions at the National meetings, the Board of Trustees have authorized the publication of a second supplement to contain papers of completed research, as presented at the Section meetings. Authors wishing publication in this supplement should send their completed manuscript and any discussion to Lorand V. Johnson, as early as possible. The absolute deadline for this supplement will be March 1. It is desired that this supplement, containing the membership roster and financial report for the fiscal year ending Dec. 31, may be published prior to the June National Meeting.

It is not possible to hold the first interim meeting in 1958, as voted by the members at the annual meeting in June, 1957. The first interim meeting will be held in 1959.

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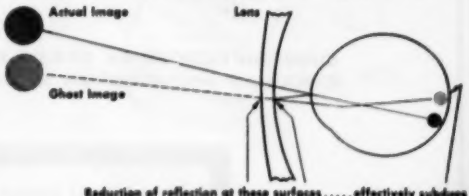

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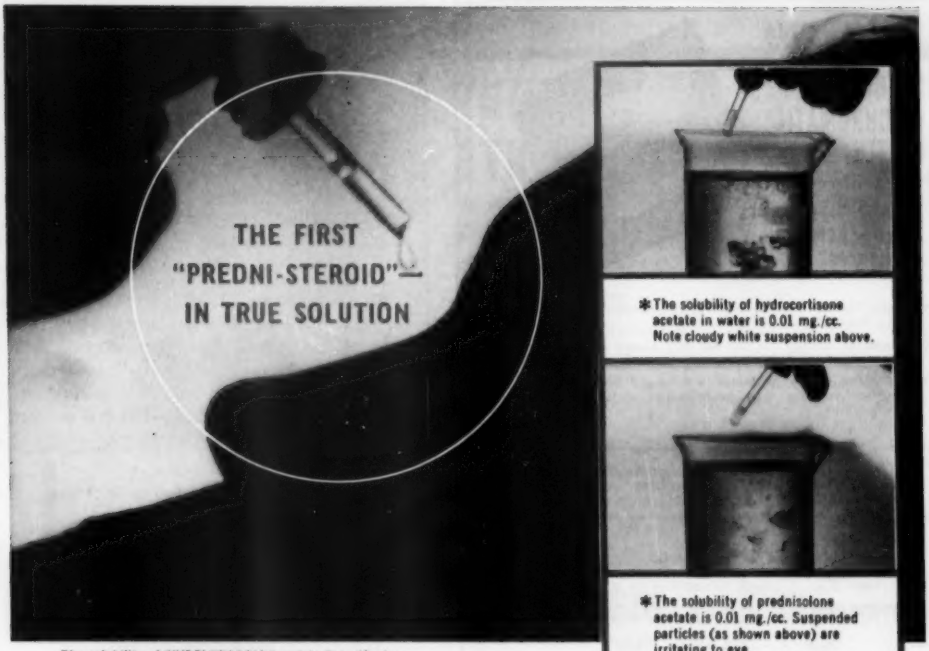

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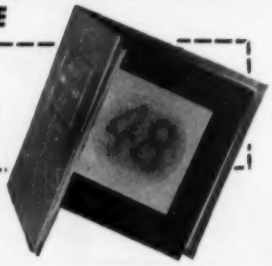

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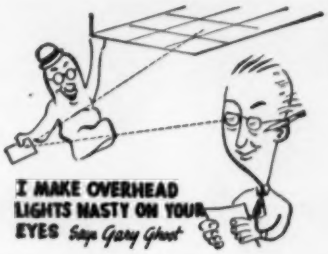

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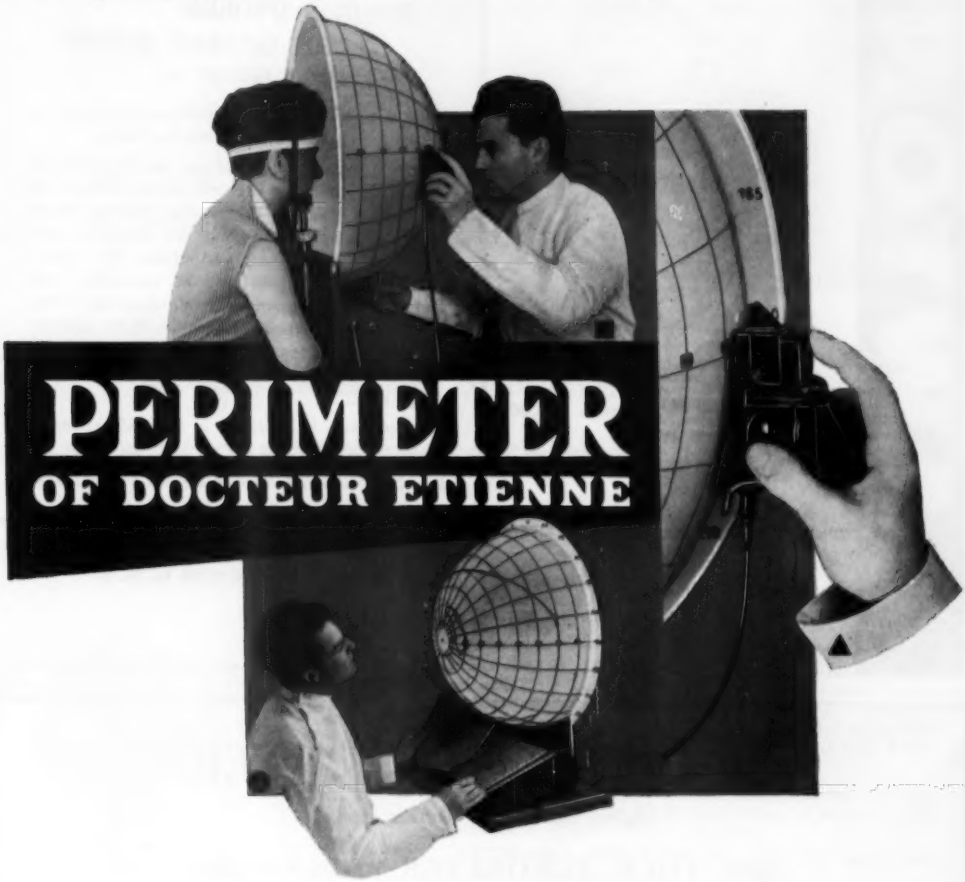

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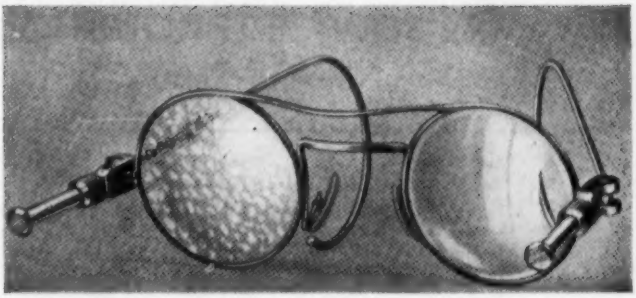

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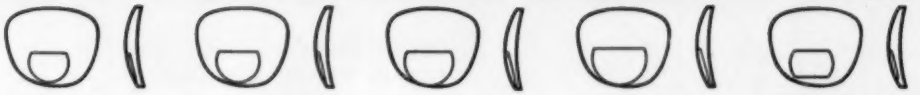

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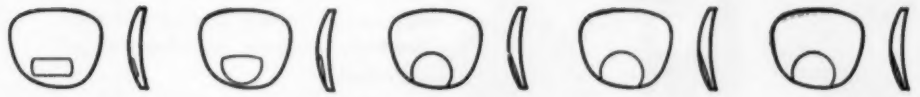

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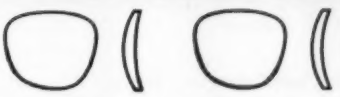

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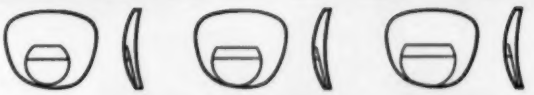

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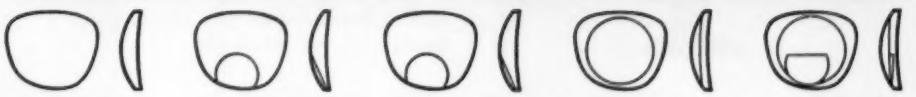

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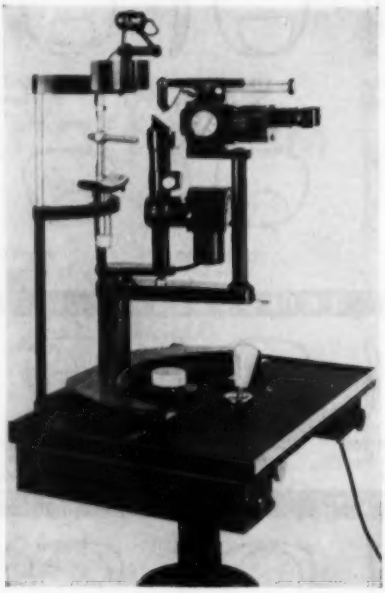

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Requires no adjustments. The slit lamp can be swung past the corneal microscope without interruption of observation.

Can be set for five different magnifications by simply turning a knob, without changing objectives, eyepieces, or the working distance.

Maximum brilliance of the illuminating rays and sharpest possible definition of the microscope images.

Supplementary equipment, such as Hruby lens, gonioscope, photo attachment, etc., are available.

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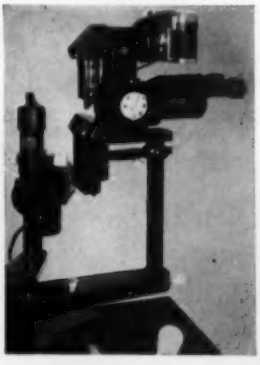
ATTACHMENT FOR GONIOSCOPY (left) consisting of: 4-mirror contact glass with handle, carrier and rotating device. Rota-table prism in mount. To keep lid apart during examination we offer one each small and large lid separator.

PHOTO ATTACHMENT (right) with electronic flash equipment to automatically photograph anterior segment of eye at magnifications of 1x or 2x.



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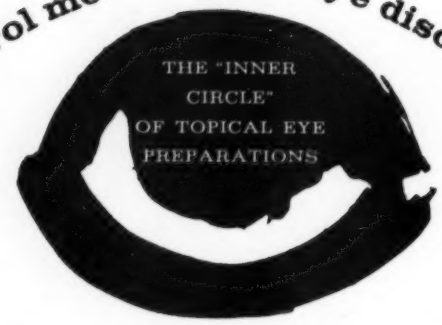

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MM-J-257

CASE HISTORY #1

The case history presented below demonstrates how Catarex Service helped the patient through the post-operative period with adequate vision.

The extreme ease with which Rx changes can be made with CATAREX T gives the patient, post-operatively, the best possible vision at all times until the operated eye has stabilized sufficiently for the final correction. And a permanent lens identical to the temporary style — CATAREX D — may be prescribed to carry through the ophthalmologist's work to its logical conclusion.

Your laboratory or optician can supply you with the details of this splendid service.

CASE HISTORY – Mr. F. S.

Mr. F.S., a 55-year-old businessman, had been aware of a gradual and painless reduction of his visual acuity for more than a year. Examination revealed cataractous changes in each lens, particularly marked in the posterior subcapsular cortex. Corrected right vision = 6/200; corrected left vision = 20/80. As this vision did not permit him to carry on with his duties, a right intracapsular lens extraction was performed on February 18, 1955. Post-operative course was uneventful and the patient was discharged on February 25th.

3-18-55: Manifest O.D. +10.50Dsph ○ +0.50Dcyl. ax 165 = 20/20—; +2.75D add = Jg. 0.75 @ 12½". Rx Right: Manifest findings in CATAREX T (temporary style) straight-top bifocal. Left: lens to balance.

4-12-55: Right vision with above CATAREX T lens = 20/40+. Manifest O.D. +10.50Dsph. ○ +1.50Dcyl. ax 105 = 20/15+; +2.75D add = Jg. 0.75 @ 13". Patient was allowed to retain first CATAREX T lens until second pair was received with new Rx.

5-5-55: Right vision with 4-12-55 Rx = 20/20. Manifest O.D. +10.00Dsph. ○ +1.50Dcyl. ax 105 = 20/15+. Again, patient was allowed to retain former lens until the new Rx in CATAREX T was ready.

5-31-55: Right vision with 5-5-55 Rx = 20/50. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 60 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-6-55: Right vision with 5-31-55 Rx = 20/20+. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 75 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-27-55: Manifest O.D. +10.50Dsph. ○ +1.25Dcyl. ax 90 = 20/15+; +2.75D add = Jg. 0.75 @ 13¾". Rx Right: CATAREX D (permanent). Left: lens to balance.

1-18-56: With permanent CATAREX D lens, right vision = 20/15+; Jg. 0.75 at 13".

The patient, who secured his first CATAREX T (temporary) bifocal lens one month after surgery and had five different Rxes in temporary lenses, secured his first and only permanent lens, CATAREX D, approximately five months after surgery; to date he has not had to have it changed or re-surfaced. Thus, the maximum visual acuity of which the eye was capable was made available to the patient during the greater part of the post-operative period by frequent changes of CATAREX T lenses as indicated, and finally by the permanent CATAREX D lens. With this lens, the patient is most comfortable ocularly at his work and contemplates having his left cataract extracted in the near future.

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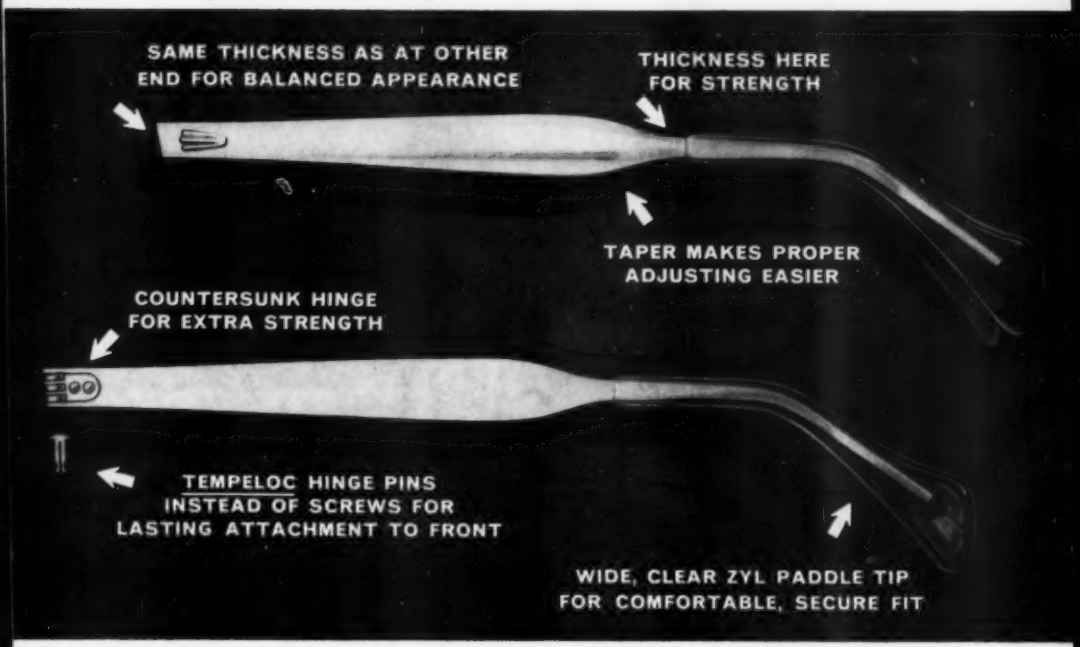
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